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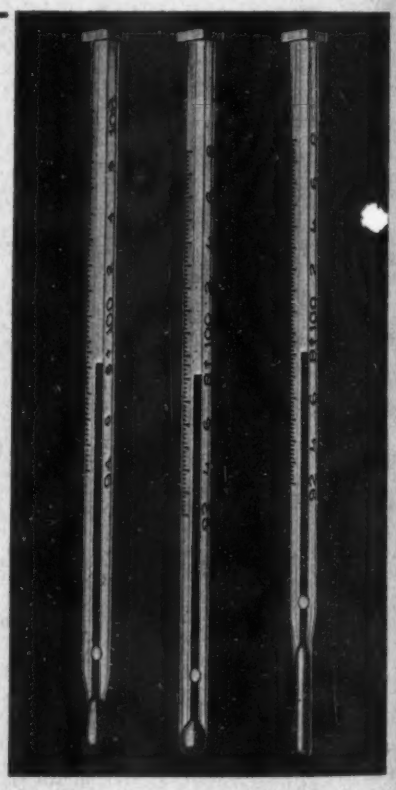

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SYPHILIS AND PULMONARY TUBERCULOSIS IN THE NEGRO[1,2]

REUBEN HOFFMAN AND GEORGE G. ADAMS

Consideration of the problem of the therapeutic attack on syphilis in the presence of tuberculosis raises many perplexing questions, few of which lend themselves to an easy solution. A cursory review of the literature reveals many contradictory reports on the relationship of the two diseases, particularly on the effect of antisyphilitic therapy in the presence of tuberculosis.

Because our sanatorium population has always shown a high percentage of syphilis, we became engaged in an attempt to put on a rational basis, if possible, the problem as it concerns our patient group. The first question for which an answer was sought was: Does the presence of syphilis influence the course of pulmonary tuberculosis in any obvious clinical manner? We emphasize the use of the phrase "obvious clinical manner," since results from limited studies of this nature cannot be expected to yield anything more than a few general facts. On the other hand, the effect of tuberculosis on syphilis is beyond our province. Indeed, Padget and Moore (1), in discussing the relationship of tuberculosis and syphilis, say that "attempts to evaluate the interaction of these two diseases in human beings are doomed to failure, by the very nature of the case."

In an attempt to obtain an answer to the above question, we compared a group of Negroes who had pulmonary tuberculosis and syphilis with a group who had only pulmonary tuberculosis. The bases for comparison were the amount of pulmonary involvement, the X-ray appearance of the pulmonary lesion and the number of deaths occurring in both groups.

The material comprises 1,705 consecutive adult admissions to the sanatorium who had pulmonary tuberculosis and on whom one or more serological tests for syphilis were performed. Patients who had more than one admission were counted as single admissions, recording their classification at the time of the first admission and their condition at the time of their last discharge.

Of the 1,705 patients with pulmonary tuberculosis, 10.3 per cent had minimal, 38.1 per cent moderately advanced and 51.6 per cent far advanced disease. Out of this group of 1,705 patients, 507 had positive serological findings, an incidence of coexisting syphilis and tuberculosis of 29.7 per cent. Guild and Nelson (2) in a survey in which 67 sanatoria participated reported an incidence of coexisting syphilis and tuberculosis among Negroes of 21 per cent and recent Maryland Selective Service figures on the incidence of syphilis among Negro selectees show 32.5 per cent.

The following figures approximate the status of the syphilis in the patients in this study: early latent syphilis (less than four years duration) 10 per cent, late syphilis (more than four years duration) 90 per cent. The group with late syphilis includes 70 per cent with late latent syphilis, 15 per cent with involvement of

[1] Read before the Eastern Section of the American Trudeau Society, New York City, January 21, 1944.

[2] From the Maryland Tuberculosis Sanatorium, Colored Branch, Henryton, Maryland.

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the central nervous system as evidenced by a positive cerebrospinal fluid, and 5 per cent with cardiovascular involvement. Almost without exception the patients gave a history of syphilis antedating the onset of the tuberculosis and about 50 per cent admitted to antisyphilitic treatment which in the great majority of cases was inadequate. No distinction has been made in this study between patients who did or did not receive antisyphilitic treatment prior to admission.

In round figures, 51 per cent of the patients were males, 49 per cent females. The distribution of these patients, according to age and sex and the percentage with coexisting syphilis, is shown in table 1.

In table 2 the 1,705 cases of pulmonary tuberculosis are divided according to their serological tests and the amount of pulmonary involvement. In table 3 the 1,705 cases are divided according to their serological tests, the amount of pulmonary involvement and the predominant type of pulmonary lesion. The percentage of deaths occurring in the positive and negative serological groups, according to the admission classification of the tuberculosis, is shown in table 4.

TABLE 1

Tuberculous patients who were diagnosed as syphilitic, classified by sex and age groups

AGE GROUP	MALE TUBERCULOUS PATIENTS			FEMALE TUBERCULOUS PATIENTS		
	Total	Diagnosed Syphilis		Total	Diagnosed Syphilis	
		Number	Per cent of total		Number	Per cent of total
All ages	873	261	29.8	832	246	29.5
15–19 years	92	7	7.6	217	37	17.0
20–29 years	293	74	25.2	339	120	35.4
30–39 years	251	88	35.0	160	57	35.6
40–49 years	141	59	41.8	76	25	32.9
50–59 years	68	25	36.7	28	4	14.3
60 years and over	28	8	28.5	12	3	25.0

It is seen from tables 2 and 3 that the amount of pulmonary involvement and the predominant type of pulmonary lesion in both the negative and positive serological groups are essentially alike. A comparison of the percentage of deaths (table 4) shows that the precentage of deaths is slightly higher in the positive serological group. Since there are nearly two and a half times as many patients in the negative as in the positive serological group, this difference has no significance.

Since most studies show that the percentage of syphilis is found to be highest in the far advanced tuberculosis group and lowest in the minimal group, the inference is drawn that the presence of syphilis unfavorably influences the ability of the patients to resist tuberculosis. In this study the figure for the percentage of syphilis in the minimal group is 24.7, in the moderately advanced group 29.2, and in the far advanced group 31.1. The difference between the percentage of syphilis in the minimal and far advanced tuberculosis groups in this study is less than 7 per cent, and is too small to ascribe to syphilis the ability

to lower the patients' resistance to tuberculosis. We feel that the patients' economic status explains this and even higher incidences more satisfactorily.

TABLE 2

1,705 cases of pulmonary tuberculosis listed according to amount of disease on admission in negative and positive serological groups

	NEGATIVE SEROLOGICAL TEST		POSITIVE SEROLOGICAL TEST	
	Number	Per cent	Number	Per cent
Minimal	131	10.9	43	8.5
Moderately advanced	460	38.4	190	37.5
Far advanced	607	50.7	274	54.0
Total	1,198	100.0	507	100.0

TABLE 3

Predominant type of lesion in the minimal, moderately advanced and far advanced tuberculosis groups in reference to the serological test for syphilis

	MINIMAL		MODERATELY ADVANCED		FAR ADVANCED	
	Negative serological test	Positive serological test	Negative serological test	Positive serological test	Negative serological test	Positive serological test
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Exudative	2.9	2.0	17.4	17.2	12.1	13.8
Exudative-productive	1.0	0.0	6.1	5.8	1.6	1.8
Productive	7.0	6.5	2.6	2.5	0.5	0.2
Cavitary	—	—	12.3	12.0	36.5	38.2
	10.9	8.5	38.4	37.5	50.7	54.0

TABLE 4

A comparison of the deaths in the negative and positive serological groups according to the admission classification of the tuberculosis

	NEGATIVE SEROLOGICAL TEST	POSITIVE SEROLOGICAL TEST*
	per cent	*per cent*
Minimal	10.8	12.8
Moderately advanced	38.2	40.4
Far advanced	72.2	74.9

* Received no or inadequate treatment before admission; none after admission.

The results of the analyses, just referred to, show that the tuberculous patients, with and without syphilis, have essentially similar amounts of tuberculosis, essentially similar distribution of the predominant type of tuberculous disease and similar prognoses. Within the limits of this study we feel justified in inferring that there is no biological relationship between the two diseases.

The problem of the coexistence of the two diseases narrows itself, therefore, to consideration of whether the syphilis should be treated for its own sake and, if treated, what modifications of the treatment, if any, should be adopted because of the presence of tuberculosis.

Certainly the choice of a patient for antisyphilitic treatment rests upon the prognosis of the tuberculosis. If the prognosis is obviously bad, then it is pointless to consider treatment of the syphilis. This decision is usually easy to make. When the prognosis is not so obvious, the choice of the patient is more difficult. There is no rule, however general, that can be applied to this problem and each patient will have to be considered individually. In practice we are influenced far more by the status of the tuberculosis than by the status of the syphilis, so that if there is a reasonable doubt about the course the tuberculosis will pursue, we withhold antisyphilitic treatment. This attitude is not a phthisiologist's bias and the stand is taken with full knowledge of the warning that "there are types of late syphilis more surely fatal if untreated than even exudative tuberculosis (for instance, aortic regurgitation, aneurysm, paresis); and other types more productive of chronic invalidism than tuberculosis (for instance, tabes dorsalis and other forms of neurosyphilis). Even in a symptomless patient apparently clinically well, the expert syphilologist can often predict with confidence that grave forms of cardiovascular or neurosyphilis will develop in the future if treatment is withheld and can guard against these developments with appropriate therapeutic measures" (1).

There are of course two conditions where antisyphilitic therapy must be employed, regardless of the outcome of the tuberculosis: in pregnancy and in the presence of the infectious stages of syphilis.

If the tuberculosis prognosis is judged good, then the patient is considered a candidate for antisyphilitic treatment, provided the status of the syphilis justifies treatment. Aside from the two conditions just mentioned (an extremely small part of the sanatorium problem), we do not institute antisyphilitic treatment, except under the following conditions: early latent syphilis when there has been no or inadequate treatment, involvement of the central nervous system, cardiovascular involvement and in those patients who, on admission, need one or two courses to complete treatment.

As for the routine treatment of late latent syphilis, we feel that there is justification both for treatment and nontreatment. That a large number of these patients, even if untreated, do well is admitted by syphilologists. Conversely, the treatment, even if interrupted and ultimately inadequate, does no harm. In our experience half of the patients with late latent syphilis enter the sanatorium either untreated or inadequately treated and the great majority fail to continue the treatment after discharge from the sanatorium. Since the patients' tuberculosis prognosis must be good before antisyphilitic treatment is instituted, the majority of these patients do not remain in the sanatorium long enough to receive what is considered minimum requirements for adequate treatment; that is, a plan of treatment that includes a minimum of twenty administrations of arsenicals (3). Therefore, the total contribution toward the "cure" of their syphilis

amounts to another episode of inadequate treatment. Yet there is the well authenticated opinion that the patient with late latent syphilis benefits regardless of the amount of treatment received.

We have vacillated between the two extremes of treating all patients with late latent syphilis and of treating none. Although there is no indecision from the medical standpoint, one wonders whether the results in this group justify routine treatment. This is a minor problem that the physician can settle to his own satisfaction.

The most important problem concerning the coexistence of syphilis and tuberculosis revolves about the potential ability of the arsenicals to flare-up tuberculosis. In fact, there would be no problem if the arsenicals were known to be harmless as far as their effect on tuberculosis is concerned. The general opinion, however, definitely ascribes to the arsenicals the ability to cause tuberculosis to exacerbate and, because of this, fractional doses of arsenicals or the use of bismuth alone are advocated.

A brief inquiry into this problem reveals that most of the opinions expressed on this subject are based on clinical impressions. A noteworthy exception is the documentary proof offered by Padget and Moore (1). They record 15 cases "in whom the sequence of events was such as strongly to suggest that the administration of an arsphenamine had provoked the flare-up and rapid dissemination of a previously quiescent and, we believe, clinically unrecognizable pulmonary tuberculosis."

An examination of their table results in the selection of at least 6 cases that we feel cannot be offered as evidence that the administration of an arsenical and the subsequent appearance of tuberculosis were cause and effect. Three cases (cases 2, 6 and 8) had no X-ray films taken before antisyphilitic treatment was instituted and thus cannot be considered at all. It is hardly necessary to state that, without an X-ray examination before treatment was started, it is impossible (unless a positive sputum was found) to say with any conviction whether tuberculosis existed and, if so, what its status was. From the photographic reproduction of X-ray films in another case (case 15), we are strongly inclined to interpret the film (showing the development of pulmonary tuberculosis three months after antisyphilitic treatment was instituted) as primary tuberculosis. This being so, the development of the tuberculosis was a matter of exposure to tuberculosis and was quite independent of the antisyphilitic treatment. Another case (case 5) is unconvincing, since symptoms appeared one week after the injection of a single dose of arsphenamine (0.3 g.) and the disease subsequently manifested itself as miliary tuberculosis and tuberculous meningitis. It seems to us more likely that the development of the tuberculous disease in this case was purely coincidental and, had antisyphilitic therapy been delayed (for some reason) for a week, the tuberculous disease would still have manifested itself. The final case (case 10) is unconvincing for the reason that too long a period of time elapsed between the beginning of antisyphilitic treatment and the onset of symptoms, namely, one year.

It is noteworthy that all the patients in Padget and Moore's series were Ne-

groes. We think that this fact should call attention to the tuberculosis hazard to which such an economic group is subjected and to the accepted fact that their resistance to the subsequent development of tuberculosis is relatively poor.

We would further emphasize that the evaluation of the effect of arsenicals on tuberculosis when applied to apparently nontuberculous patients attending a venereal disease clinic includes factors that differ when applied to patients with frank pulmonary tuberculosis in a sanatorium. In the former group, the appearance of active tuberculosis may be due to one of two causes: either the lighting-up of an unrecognizable (or unrecognized) lesion or the coincidental development of tuberculosis through superinfection. Without an intimate knowledge of the patient's tuberculosis hazard, the answer can never be definitely known and, even if all factors are considered, the answer will have the nature of a surmise. In the latter group, the ever-present explosive qualities of tuberculosis make the evaluation of any suspected causative factor dubious.

In our experience, we have encountered but one patient in whom the sequence of events was so striking, following one course of mapharsen, that we were forced to incriminate the arsenical. In all other cases where the tuberculosis became worse under antisyphilitic treatment, we could only surmise whether the arsenic or some other factor was responsible or whether the flare-up was spontaneous. In some of our patients, the tuberculosis flared up when bismuth was the only drug used.

We do not wish to imply that the use of arsenicals does not cause tuberculosis to flare up. We hold that proof of such an action is extremely difficult and that few have offered convincing evidence that it was the cause in any one particular case. To us, the question is wide open and merits serious consideration and study by those interested in the problem.

Animal experimentation offers very little help, since experimental syphilis and tuberculosis in a rabbit can hardly be applied to human beings. One report in this connection was made by Aronson and Meranze (4) who concluded "that local experimental tuberculosis pursues an identical course in untreated syphilitic rabbits and in syphilitic rabbits treated with treponemicidal doses of arsphenamine."

We have not encountered any convincing evidence that fractional doses of an arsenical are any less likely to flare up tuberculosis than a full dose and therefore feel that there is no rationale in its use. More important, however, is the fact that fractional doses of an arsenical vitiates the purpose for which the antisyphilitic treatment was instituted, that is, "cure" of the syphilis. The case against fractional doses is well epitomized by Padget and Moore (1): "Such mild treatment, while of benefit to the allergic inflammatory lesion of patients with late syphilis, cannot be considered even palliative for certain forms of neurosyphilis, for example, and, according to present standards, is totally inadequate for the 'cure' of early syphilis and in many instances for the prevention of infectious relapse." Because of the above facts, we have, from the beginning, used the conventional doses of arsenicals.

The number of patients we have treated for syphilis has been small (about 150),

because our selection of patients has been and still is severely limited by the high percentage of moderately and far advanced active tuberculosis seen in our admissions. Guided by the clinical impression, which was subsequently confirmed by this study, that the tuberculosis is not affected by the presence of syphilis and influenced by the knowledge that inadequate treatment for syphilis is the customary outcome, we have probably still further reduced the available number of patients who could have been treated.

As for the effect of antisyphilitic therapy on the progress of the syphilis, there is hardly anything to say. The aim of treatment in early syphilis is "cure." The aim of treatment in late syphilis is maintenance of well-being, the prolongation of life in the presence of cardiovascular syphilis, and a reversal or improvement in the cerebrospinal fluid in the presence of involvement of the central nervous system. The final evaluation of these aims is obviously out of the reach of the sanatorium and a job for the syphilologist. If the patient does not succumb to his tuberculosis, we will have to wait five to ten years to hear what the syphilologist has to say about these patients.

The fact that tuberculosis is one of the diseases listed as causing false positive reactions for syphilis has been kept in mind. In a very limited manner, we attempted to find out how often a reported positive serological test might be due to the presence of tuberculosis and not to syphilis. For this purpose we chose patients who denied a history of syphilis, whose admission serological test was negative and who were running a temperature, during the study, of 101°F. or more. Even though in Parran and Emerson's study (5) false reactions occurred with equal frequency in patients with or without fever, we limited our study to patients who were febrile, many markedly so. The serological tests were repeated at regular intervals for a specified number of times or until, in some instances, the patient died. In addition, we selected all patients who in the previous six years had serological tests for syphilis repeated at varying intervals, or who had more than one admission with serological tests performed at each admission. This group is also limited to those who were febrile, although in some instances the fever was low-grade. In a few patients the disease was minimal and patient afebrile at first admission; markedly febrile, toxaemic and the disease terminating fatally at the second admission.

Table 5 lists the interval and the number of times the serological tests were repeated. In the total number of 239 serological tests performed on 69 patients, a positive report was obtained in only 2 instances. In one patient a positive report (3 precipitation tests, 2-plus) was followed by 3 negative tests in twenty-seven days and a final negative test fourteen months later. Since there was no history of syphilis, this was interpreted as a technically false positive reaction. In the other case, the patient denied a history of syphilis and his admission serological test was negative. Patient had primary tuberculosis, did well for about six months and then showed signs of reinfection disease. At this time he developed an ocular lesion and was referred to another hospital. At the latter place, his serological test was negative. On returning to the sanatorium the patient ran a temperature that averaged 103°F. and an X-ray film showed massive

involvement of one lung and beginning involvement of the other lung. A serological test was performed which was reported as positive. Unfortunately, the patient died three days after this test and no check examination was possible. The laboratory report was "positive Hinton; insufficient serum for a check examination; specimen haemolyzed." This was likewise considered a technically false reaction.

This analysis is by no means meant to be an inquiry into the question of false serological reactions for syphilis in the presence of tuberculosis. The number of patients and the number of repeat examinations are too few for us to offer any opinion. The study simply suggests that, with careful history taking, careful diagnostic procedures[3] frequently repeated when in doubt (and properly interpreted), the problem is not important.

TABLE 5

Showing the number of times and the intervals that the serological test for syphilis was performed in 69 patients

	NUMBER OF CASES REPEATED			
	2 times	3 times	4 times	5 times
Serological test on admission and 14 day repeats..	2	6	2	18
Serological test on admission and 7 day repeats ..				8
Serological test on admission and repeated at random intervals.....	25	4	3	1

DISCUSSION

One of the questions which will be asked is what were the criteria for the selection of those cases labelled syphilis in this study? In about half of the patients a single positive serological test was the sole evidence; in the remaining half, either two positive serological tests or one positive serological test and a history of syphilis. When the serological test was reported one or more times as doubtful (or 1 or 2 plus) and when there was no confirmatory history, the case was excluded. It is the accepted opinion that the diagnosis of syphilis can be made with a 90 per cent accuracy on the basis of positive serological tests alone. Since a part of this study indicated that tuberculosis hardly ever is the cause of a false positive reaction for syphilis, we feel that we have not included any nonsyphilitics. Actually, we encountered 102 patients with a history of syphilis whose serological tests were reported as negative on one or more occasions. Not being certain how to classify these patients, we excluded them from this study.

We have purposely excluded any report on the outcome of the tuberculosis in those patients who received antisyphilitic treatment. Since the group receiving treatment was selected because their tuberculosis prognosis was good, comparison with an unselected group of tuberculous patients with syphilis who did not receive antisyphilitic treatment could be of no value.

Many of the questions that come to mind in considering the dual problem of syphilis and tuberculosis are extremely difficult to answer and are due to the com-

[3] All the serological tests were performed at the Maryland State Department of Health.

plex factors inherent in two chronic diseases such as these. The problem of the effect of the arsenicals on tuberculosis, by all odds the most important, appears to actually defy solution.

Most studies on coexisting syphilis and tuberculosis, including this one, encompass a group of patients too small to allow the expression of a definite opinion on the interrelationships that may exist between the two diseases. What is obviously needed is a careful study of large numbers. Such a study had been planned by the United States Public Health Service coöperating with the Committee on Coexisting Syphilis and Tuberculosis of the American Trudeau Society, but had to be postponed because the sanatoria planning to participate had found the task too great for their reduced war staffs. It is hoped that this study will be found on our postwar agenda.

SUMMARY

To determine the effect of syphilis on tuberculosis, 507 Negro patients with tuberculosis and syphilis were compared with 1,198 patients with only pulmonary tuberculosis. The bases for comparison were the amount of pulmonary involvement and the predominant type of tuberculous lesion that these two groups exhibited on admission and the percentage of deaths occurring in both groups in relation to the admission classification of the tuberculosis (no treatment being given for the syphilis). The analysis showed that there was no significant difference in the amount of pulmonary disease, the predominant type of tuberculous lesion or the percentage of deaths in the negative and positive serological groups. Further, the difference in the percentage of syphilis between the minimal and far advanced tuberculosis groups was less than 7 per cent and could not be used to infer that syphilis lowered the resistance of a patient to tuberculosis.

From these two analyses it was considered justifiable to conclude that the presence of syphilis does not alter the course of pulmonary tuberculosis.

Before a tuberculous patient is subjected to antisyphilitic treatment, his tuberculosis prognosis must be good. The presence of pregnancy and contagiousness (syphilitic) are the only exceptions. If the tuberculosis prognosis is good, the syphilis is treated, provided that certain criteria for treatment are met, such as early latent, cardiovascular and central nervous system involvement. Whether late latent syphilis should be routinely treated is left an open question.

An inquiry into the effect on the use of arsenicals in the presence of tuberculosis was made. Attempts were made to show that proof that the use of an arsenical flares up tuberculosis in any one case is extremely difficult, if not impossible.

The aims of antisyphilitic treatment are stated and it is pointed out that the use of fractional doses of arsenicals (used because it is feared that full doses may activate tuberculosis) is empirical and defeats the purpose for which antisyphilitic treatment was instituted, that is, "cure" of the syphilis.

Some of the problems associated with the coexistence of these two diseases are outlined and the need for a careful study of large numbers is stressed.

The question of the false biological reaction for syphilis in the presence of tuberculosis is briefly considered.

SUMARIO

A fin de determinar el efecto de la sífilis sobre la tuberculosis, se comparó a 507 negros que padecían de tuberculosis y sífilis con 1,198 que sólo padecían de tuberculosis pulmonar. Como bases de comparación se tomaron la invasión pulmonar y el tipo predominante de lesión tuberculosa que mostraban ambos grupos a su ingreso y el porcentaje de mortalidad en relación con la clasificación de la tuberculosis al ingreso (sin facilitarse tratamiento para la sífilis). El análisis demostró que no había mayor diferencia en la intensidad de la afección pulmonar, el tipo predominante de tuberculosis y el porcentaje de mortalidad en los grupos de serología negativa y positiva. Además la diferencia en el porcentaje de sífilis entre los grupos de tuberculosis mínima y avanzada fué inferior a 7 por ciento, y no pudo usarse para deducir que la sífilis mermara la resistencia de un enfermo a la tuberculosis.

Por esos dos análisis se consideró justificado deducir que la presencia de sífilis no modifica la evolución de la tuberculosis pulmonar.

Antes de someter a un tuberculoso al tratamiento antisifilítico, el pronóstico debe ser bueno en cuanto a tuberculosis, correspondiendo las únicas excepciones a la presencia de embarazo y de contagiosidad (sifilítica). Si el pronóstico es bueno con respecto a la tuberculosis, se trata la sífilis con tal que se observen ciertas pautas terapéuticas, como son las relativas a invasión del aparato cardiovascular y del sistema nervioso central y presencia de sífilis temprana. Queda sobre el tapete la cuestión de si se debe o no tratar sistemáticamente la sífilis tardía.

También se investigó el efecto del empleo de los arsenicales cuando había tuberculosis presente, haciéndose esfuerzos para demostrar que es sumamente difícil si no imposible obtener pruebas de que el empleo de un arsenical exacerba la tuberculosis en cualquier caso dado.

Enuméranse los propósitos del tratamiento antisifilítico, señalándose que la utilización de dosis fraccionadas de arsenicales (por temerse que las dosis enteras pueden activar la tuberculosis) es empírica y anula el fin para el cual se instituye el tratamiento antisifilítico, o sea la "curación" de la sífilis.

Bosquejánse también algunos de los problemas derivados de la coexistencia de las dos dolencias, recalcándose la necesidad de verificar un estudio cuidadoso de un gran número de enfermos.

Considérase sucintamente la cuestión de las seudo-reacciones biológicas de sífilis cuando existe tuberculosis.

Acknowledgment

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NUTRITION IN TUBERCULOSIS AS EVALUATED BY BLOOD ANALYSIS[1,2]

HORACE R. GETZ, IRENE S. WESTFALL AND HOWARD J. HENDERSON

This paper records the results of a nutritional study of 457 tuberculous and nontuberculous patients attending an out-patient chest clinic. In the majority a single assay was performed; in a number, however, multiple examinations over a prolonged period were made, bringing the total number of nutritional assays to 513. Each nutritional assay included a determination of blood haemoglobin, serum proteins, plasma carotene, serum calcium, serum phosphorus and serum phosphatase, as well as plasma ascorbic acid, vitamin A and erythrocyte sedimentation rate. Preliminary studies have already been reported (1, 2).

In the following pages correlations are made of the analyses with the presence or absence and character of tuberculosis, and of the individual deficiencies with each other.

The tests on each patient were all made on one specimen of blood. A few subjects were observed several times and the findings are included. There was no obvious selection of the persons on whom multiple observations were made, as they were tested as they returned to the clinic, usually after an interval of several months. These would ordinarily be excluded when calculating the incidence of nutritional deficiencies in the subjects. However, the sampling appears still representative, as indicated by the finding of essentially the same extent of the deficiencies of vitamins A and C as was previously reported for this population group (1, 2).

The subjects were all males in the age group twenty to forty-five years inclusive, except for a few females who were included for the correlation studies but excluded in the studies of incidence of deficiencies (tables 2 and 3). The study was limited to males in order to exclude the disturbing influence of reproduction and the sexual cycle on the nutritive status. Race seemed to make no difference in the correlations, so that all observations could be pooled for correlation studies. Forty-one per cent of the subjects were Negroes. The population studied resides in the underprivileged areas of Philadelphia, where both tuberculosis and malnutrition are known to be prevalent.

METHODS

The blood for the tests was drawn between 10 and 11 a.m., as a rule, by venipuncture into syringes well oiled with heavy mineral oil to reduce the possibilities for haemolysis and aeration. The sample was then divided, a portion being allowed to clot to obtain serum and the rest oxalated to obtain plasma. The sedimentation of the erythrocytes was determined by the Cutler (3) method of noting the maximum drop in any five-minute period. The total drop in one hour was also noted, but not used in analyzing results, for it did not show consistent and characteristic relationships as did the maximum five-

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minute drop. Blood haemoglobin was determined in the photoelectric colorimeter by the method of Evelyn (4). Vitamin A and carotene in the plasma were determined by the Kimble (5) modification of the Dann and Evelyn method, which employs the Carr-Price reaction and the photoelectric colorimeter. Plasma ascorbic acid was determined by reduction of 2, 6 dichlorophenolindophenol with metaphosphoric acid plasma filtrates in the Evelyn colorimeter. The method combines features of the techniques of Mindlin and Butler (6) and Evelyn, Mallory and Rosen (7). Total serum proteins were determined by the photoelectric biuret method of Kingsley (8). Serum albumin was determined after the globulin was precipitated and removed. It was determined colorimetrically (9) as total protein, and the globulin then calculated by the difference. The albumin-globulin ratio was computed and recorded. Serum calcium was determined by the Clark and Collip (10) modification of the Kramer and Tisdall method, using the permanganate titration of the calcium oxalate precipitate from the serum. Serum inorganic phosphorus was determined by the photoelectric modification of the Fiske and Subbarow (11) method. Serum phosphatase activity was determined by the Karr, Reinhold and Charnock (12) modification of the Bodansky method.

To facilitate the handling of the data, all observations on one specimen were transferred to punch cards (International Business Machines Company) together with general information including the subject's age, diagnosis, height, weight, per cent of standard weight, temperature, sex and race. Thus it was possible quickly to obtain all the data for any group of observations desired; for example, the low serum calcium observations could be sorted out and the rest of the data on the same blood compiled quickly in a listing tabulator. The data were analyzed by using arithmetic means, medians and percentage distribution of the observations in the various blood levels for each substance tested, and finally they were tested for statistically significant correlations by using the chi-square formula on contingency tables.

EXTENT OF MALNUTRITION

In order to appraise the nutritive status of our population, some levels had to be chosen as the normal physiological level for each test used. There is still insufficient knowledge on this subject for one to be certain that any chosen level is "normal," but the levels chosen served our present needs and gave a basis on which to make comparisons. Most of the "normal" levels chosen represent accumulated knowledge, but the levels of vitamin A are our own selection (1). Table 1 gives the percentage of observations in the normal zones for the nontuberculous population. Table 2 gives the percentage distribution of all observations on the tuberculous and nontuberculous for each of the designated blood levels. Table 3 gives the medians of the observations for direct comparison with other populations. This table also gives an impression of the general level of each of the nutrients in the blood of our subjects, as one-half of the observations are above *and* below the median figure. The median is especially of value in giving a picture of the amount of ascorbic acid in the subjects with far advanced tuberculosis. The punch cards were arranged in ascending values of ascorbic acid and the middle card, the median, was pulled out. The value for ascorbic acid was zero for that specimen of blood. This meant that all of the cards in front of the median card also had recorded values of ascorbic acid of zero, and possibly a few cards on the other side of the middle card. In this instance then,

the median gives information on the shape of the frequency distribution curve which is not evident in table 2. The median was not as helpful with the ascorbic acid values on the other tuberculous patients. The values appear to indicate that the tuberculous patients were better in ascorbic acid than the nontuberculous subjects. All of the subject groups showed extensive and severe ascorbic acid deficiency, so that slight fluctuation of the average levels is not significant. Undoubtedly larger numbers of tuberculous subjects would have given a more nearly true statistical picture as shown by the median. Likewise the median of the calcium observations on the subjects with far advanced tuberculosis is misleading, and calcium levels are better portrayed in table 2. Of those with low levels there were relatively few with levels of calcium approximating the normal. The calcium level was either normal or low.

TABLE 1

Extent of malnutrition in nontuberculous populations

TEST	PERCENTAGE WITHIN NORMAL RANGE	DEFINITION OF NORMAL
Sedimentation rate	81	1 mm. maximum drop in 5 minutes
Ascorbic acid	4 or 19*	1.0 mg. per cent and up or 0.5 and up
Vitamin A	41	110 and up Int. Units per 100 cc. plasma
Carotene	62	0.11 mg. per cent and up
Haemoglobin	38	15.4 g. per cent and up
Albumin	46	4.5 g. per cent and up
Globulin	63	1.8–2.9 g. per cent
Albumin-globulin ratio	45	1.65 and up
Per cent standard weight	64	90–110 per cent
Phosphorus	77	3.0–4.5 mg. per cent
Phosphatase	86	1.5–4.0 mg. per cent
Calcium	95	9–11 mg. per cent

* According to which standard is used (1.0 mg. per cent and up or 0.5 mg. per cent and up).

The state of nutrition in those who stated they were taking one pint of milk a day was compared with that of those drinking less than that amount. The numbers of observations totaled 248 and 196, respectively. There was a slight indication that those with the extra milk were superior in nutritive status to those with less milk, but the difference cannot be attributed to the milk only, as no control was made of the other variables. Those who consumed at least a pint of milk had higher average blood levels. The following figures give the values obtained, the first in each instance being the average figure for those drinking one or more pints of milk a day: vitamin A, 97.8 and 94.3 I.U. per 100 cc. plasma; carotene, 0.12 and 0.11 mg. per cent; albumin-globulin ratio, 1.77 and 1.6; calcium, 9.64 and 9.48 mg. per cent.

A similar comparison was made of those observations on the subjects taking codliver oil or supplementary vitamin preparations, but it revealed that they had

TABLE 2

Percentage distribution according to test group and diagnoses

TEST GROUP	NONTUBERCULOUS (266)	ACTIVE PULMONARY TUBERCULOSIS			QUESTIONABLY ACTIVE, MIN. & MOD. ADV. (62)	ARRESTED, MIN. & MOD. ADV. (18)
		Minimal (37)	Moderately advanced (34)	Far advanced (26)		
Sedimentation rate:						
1 mm.	81%	51%	30%	8%	72%	82%
2–4 mm.	16	35	58	44	25	18
5–9 mm.	3	14	9	28	3	0
10+ mm.	0	0	3	20	0	0
Ascorbic acid:						
1.0 mg. per cent and up	4%	0%	9%	4%	9%	11%
0.5–1.0	15	19	28	9	11	28
Below 0.5	81	81	63	87	79	61
Vitamin A:						
110 I.U. per 100 cc. and up	41%	25%	24%	15%	27%	39%
85–110	32	36	24	15	33	28
Below 85	27	39	52	70	40	33
Carotene:						
0.11 mg. per cent and up	62%	55%	64%	15%	58%	61%
Below 0.11	38	45	36	85	42	39
Haemoglobin:						
15.4 g. per cent and up	38%	31%	26%	12%	46%	41%
12.4–15.4	60	66	68	48	48	59
Below 12.4	2	3	6	40	6	0
Albumin:						
4.5 g. per cent and up	46%	36%	44%	8%	52%	72%
4.0–4.5	37	39	38	32	36	17
Below 4.0	17	24	19	60	12	11
Globulin:						
3.0 g. per cent and up	37%	64%	53%	84%	42%	33%
2.5–2.9	42	30	25	8	39	22
1.8–2.4	21	6	16	8	19	44
Below 1.8	1	0	6	0	0	0
Albumin-globulin ratio:						
1.65 and up	45%	18%	34%	4%	41%	61%
1.3–1.65	39	46	44	20	42	17
Below 1.3	16	36	22	76	17	22
Per cent standard weight:						
Above 110 per cent	15%	2%	0%	0%	8%	6%
90–110	64	55	24	50	56	24
Below 90	21	43	76	50	35	71

TABLE 2—*Concluded*

TEST GROUP	NONTUBERCULOUS (266)	ACTIVE PULMONARY TUBERCULOSIS			QUESTIONABLY ACTIVE, MIN. & MOD. ADV. (62)	ARRESTED, MIN. & MOD. ADV. (18)
		Minimal (37)	Moderately advanced (34)	Far advanced (26)		
Phosphorus:						
4.5 g. per cent and up	7%	6%	3%	4%	3%	0%
3.75–45	26	39	27	15	24	25
3.0–3.75	51	46	61	65	60	69
Below 3.0	16	9	9	15	13	6
Phosphatase:						
Below 1.5 mg. per cent	10%	6%	6%	8%	10%	6%
1.5–2.75	60	52	67	46	67	44
2.75–4.0	26	27	27	31	14	31
4.0 and above	4	15	0	15	10	19
Calcium:						
Above 11 mg. per cent	1%	0%	0%	0%	0%	0%
9–11 mg.	95	91	97	77	95	94
Below 9	4	9	3	23	5	6

TABLE 3

Medians for each test according to nontuberculous and tuberculous diagnoses

TEST	UNIT	NONTUBERCULOUS	ACTIVE REINFECTION TYPE TUBERCULOSIS		
			Minimal	Moderately advanced	Far advanced
Sedimentation rate	mm. in 5 min.	1	1	2	4
Ascorbic acid	mg. per cent plasma	0.10	0.21	0.16	0.00
Vitamin A	I.U. per 100 cc. plasma	99.0	89.0	84.0	54.0
Carotene	mg. per cent plasma	0.12	0.11	0.12	0.07
Haemoglobin	g. per cent blood	15.1	14.8	14.5	13.2
Albumin	g. per cent serum	4.4	4.3	4.4	3.9
Globulin	g. per cent serum	2.75	3.1	3.0	3.7
Albumin-globulin ratio		1.6	1.35	1.4	1.1
Per cent standard weight		98.5	91.5	92.0	89.0
Phosphorus	mg. per cent serum	3.5	3.7	3.45	3.4
Phosphatase	mg. per cent serum	2.4	2.5	2.4	2.7
Calcium	mg. per cent serum	9.6	9.6	9.8	9.55

poorer levels of almost everything, probably because 44 per cent of these observations were made on tuberculous subjects. They had developed the practice of taking extra vitamins and in most instances before they knew they had tuberculosis.

Observations made on patients who had breakfast as compared with observations on those that fasted revealed almost no difference in the group averages.

Vitamin A and ascorbic acid observations were slightly higher in those that had breakfast. The values follow, the first figure in each instance being the average of the observations on subjects with breakfast: vitamin A, 97.0 and 94.6 I.U. per 100 cc. plasma; ascorbic acid, 0.27 and 0.23 mg. per cent.

Eighty-one observations were made on patients with fever. When the data are compared with those for persons with a normal temperature (328) we have (first figures average of those with fever): sedimentation rate, 2.9 and 1.7 mm.; haemoglobin, 14.4 and 14.8 g. per cent; vitamin A, 89.6 and 96.6 I.U. per 100 cc. plasma; carotene, 0.11 and 0.12 mg. per cent; ascorbic acid, 0.25 and 0.26 mg. per cent; albumin-globulin ratio, 1.46 and 1.59; total protein, 7.4 and 7.2; phosphatase, 2.63 and 2.42 mg. per cent. Observation of other nutritional characters revealed no differences in the two groups. One-quarter of those with fever had active tuberculosis; when these were removed the differences were still present but to a lesser degree.

Extent of malnutrition in the different age groups is discussed later.

CORRELATION STUDIES

All of the findings, except total serum protein, serum calcium and serum phosphorus, show a positive correlation with tuberculosis when the nontuberculous group is used for a basis. Both tuberculous and nontuberculous subjects exhibited the same nutritional deficiencies; in the tuberculous they were of profound degree (tables 2 and 3). A number of deviations in the extent of the deficiencies is hardly noticeable, except when examining the group with far advanced tuberculosis. Sedimentation rate, vitamin A, carotene, ascorbic acid, albumin-globulin ratio, albumin and haemoglobin levels all were progressively worse with the advancement in the stage of the disease. Globulin values increased with the stage of the disease Albumin and globulin correlations are not shown in a separate table, as they are included in other tables. It is interesting to note in table 2 how the figures for the arrested cases approximate those for the nontuberculous population. The stage of advancement of tuberculosis was greater with advancing average age. The average age was 31.8 years for the active minimal cases of tuberculosis, 32.7 for the active moderately advanced, and 34.1 years for the active far advanced cases. The average age for the arrested cases was 37.3 years.

All statistical analyses that were made with the sedimentation rate as the primary factor show a positive correlation. These correlations are with plasma ascorbic acid, serum albumin and globulin, serum albumin-globulin ratio, plasma vitamin A and carotene, serum phosphatase and blood haemoglobin and with the presence of tuberculosis. The latter shows statistically significant changes even with the minimal cases, where the changes are not as obvious as with the more advanced stages. The sedimentation rate also shows a positive correlation with age (table 6); the greater the age, the higher the percentage of persons with a high sedimentation rate. There is also a positive correlation between the sedimentation rate and the per cent of standard weight; the higher the per cent of standard weight, the higher the percentage of persons with normal sedimentation rates.

With blood haemoglobin we found a positive correlation with plasma vitamin A, ascorbic acid and carotene, serum albumin, albumin-globulin ratio, serum phosphatase, sedimentation rate, per cent standard weight and tuberculosis. The extent and direction of the correlations are shown in table 5. There seems to be no correlation of haemoglobin and age. It is the outstanding negative correlation of the study.

Most of the subjects studied were between the ages of twenty and forty-five years inclusive—our predetermined age group—but a few were observed under and a few above these limits. The subjects used in the age correlation studies were twenty to forty-nine years inclusive, an age span presumably too short to depict all the age changes that take place. We found positive correlations (table 6) of age and sedimentation rate, plasma vitamins A and C, carotene and albumin-globulin ratio, and found a negative correlation with blood haemoglobin.

SPECIFIC FACTORS STUDIED

Ascorbic acid: Our data show again that subnormal ascorbic acid is the most conspicuous deficiency of both our tuberculous and nontuberculous subjects. The deficiency is worst in the far advanced tuberculous group, where 87 per cent are deficient (table 2). In tables 1 and 3 it is evident that using the higher standard of 1.0 mg. per cent as the lowest limit of normal, only 4 per cent of the nontuberculous population meet this requirement. If one uses the more lenient but less justified level of 0.5 mg. per cent as the lower limit of normality, only 19 per cent of our nontuberculous males meet this standard. We believe the 0.5 mg. per cent standard is not justified, as we have found that our control subjects—staff members—have levels of ascorbic acid above 1.0 mg. (1) when eating the usual amounts of ascorbic acid. We feel that the plasma level of ascorbic acid is what we need to judge the nutritive status. Scurvy is seldom seen in our clinic. It is probably the result of a number of factors of which ascorbic acid depletion is only one. The plasma level seems to reflect the average intake, and gives some indication of the stores. This lack of ascorbic acid in our population seems to be due to failure to eat fruits, and citrous fruits in particular, since the vegetable consumption of our nontuberculous population appears to be adequate, as evidenced by the normal level of carotene, which was found to be almost identical with the average level of carotene in our staff subjects. The plasma level of carotene is good evidence of the vegetable consumption, as little of it comes from other sources.

Haemoglobin: According to our findings (table 1), the next most serious deficiency of our population is reflected by the comparatively low percentage of normal haemoglobin observations. Again the tuberculous subjects had the lowest levels. The deficiency is progressive with the advancement of the stage of the disease; it is profound in the far advanced cases, where 40 per cent had levels below 12.4 g. per cent (table 2). As with ascorbic acid, the deficiency is less evident in the arrested cases. The correlations revealed in table 5 show that our patients with definite anaemia are patients with multiple deficiencies. Those with the highest level of haemoglobin, on the other hand, have remarkably good values in the other tests. This observation emphasizes the value of the haemo-

globin test, for, if it reveals a low blood haemoglobin, other nutritional deficiencies may be expected.

We feel the standard of 15.4 g. per cent is high for our community and the physiological needs of our subjects, but when one looks further (table 2) and finds that 60 per cent of the observations on the nontuberculous subjects fall between 12.4 and 15.4 g., the need of the population seems certain. The fact that the haemoglobin concentration in one-half of the observations on these patients is above 15.1 g. per cent (table 3) seems to support the use of the 15.4 g. per cent standard. A number of factors undoubtedly are active in lowering the level of haemoglobin in our nontuberculous population, of which protein and iron nutrition are only two. Our population is short of protein as shown by the serum albumin findings. The significance of mild anaemia, as evidenced by slightly lowered blood haemoglobin, is not definitely known. The same is true for mild deficiencies of the other nutrients, but clinicians have long been aware of the improvement noted by patients who have had a mild anaemia ameliorated. Mackay and Goodfellow (13) have gone one step further and studied the significance of haemoglobin levels in newborn children. One of the two groups received extra iron. At the end of twelve months they had a mean haemoglobin 13 per cent higher than the control group, and they also had about one-half the morbidity, and averaged a pound heavier. If this work is confirmed by others, it will lend support to a more serious consideration of the mild anaemias. It is unsafe to infer that the work on children can be applied to adults, but it may point the way for other investigations.

After studying the data one wonders if it is possible to find a subject with an anaemia only. The data indicate that such persons are rare. This suggests that nonspecific treatment of cases of anaemia to alleviate other nutritional deficiencies may be important. The data here obtained may explain the decreased effect of iron therapy in donors giving four and five blood donations, as noted by Fowler and Barer (14, 15). The frequency and severity (in our population) of other deficiencies with anaemia suggest that active therapy for these is necessary. This should supplement dietary programs such as that of McKibbin and Stare (16).

Vitamin A: Vitamin A is the next most noticeable deficiency in our population. If the standard of normality were a little more generous for haemoglobin, vitamin A deficiency would rank second to ascorbic acid deficiency. The level of plasma vitamin A parallels closely the extent of the tuberculous involvement (tables 2 and 3). This was reported previously (1, 2), but the observations on the arrested cases complete the picture (table 2). These findings may have particular import in tuberculosis, as vitamin A has long been designated the anti-infective vitamin and recently has been ascribed functions relative to normal phagocytosis (17). The observation that the arrested cases are better nourished (even though thin) than the active cases of tuberculosis brings up the question of the importance of nutrition on the course of the disease. Was the superior nutritive status a factor in recovery or did improved nutritive status merely follow the cessation of the disease process?

We first reported finding vitamin A deficiency in tuberculous subjects by use

of the biophotometer (18), but we now use the plasma level, as it is more objective. Breese, Watkins and McCoord (19) have confirmed the finding of vitamin A deficiency in tuberculous subjects by an intestinal absorption test based on plasma vitamin A determinations. Some hold that the plasma level is not suitable to make a diagnosis of vitamin A deficiency. It is true that it does not give us the exact extent of the vitamin A stores, but it does give us more than the exact status of the blood at the time the determination was made. Given an observation of 125 I.U. of vitamin A per 100 cc. plasma, we know that the subject on whom the observation was made had a good physiological level at the time of sampling and probably had reasonably good stores. The vitamin A level of the blood is a fairly stable factor and is not changed greatly from day to day. Given an observation of 50 I.U. of vitamin A per 100 cc. of plasma, we know that the subject is not eating enough vitamin A and also that his body stores are not good enough to hold the blood level up to the normal level. These statements are supported by observations made on the plasma level of a vitamin A-fasting subject who previously was well saturated with vitamin A (20). The plasma level was maintained at 126 I.U. (average) per 100 cc. of plasma in the first six months of fasting, at 113 I.U. during the next six months and at 102 I.U. during the rest of the fasting, making a total of one year, eight months and fifteen days in which the body stores maintained the plasma level over 100 I.U. per 100 cc. It is clear from these results that the plasma level gives a fair idea of the reserves and not merely the status at the time of observation.

Our data, interpreted in the light of what has just been said, will not support the belief stated in Nutrition Reviews (21) that infection (or fever) impairs the mobilization of vitamin A. Tuberculosis, when it is progressive (usually with associated fever) causes rapid lowering of the vitamin A plasma levels and at death the liver has low levels of vitamin A (22). It seems more probable that infection, with fever, and the accompanying increased metabolic rate use up more vitamin A. The temporary drop of plasma vitamin A observed in short term infections may be due to failure to meet the accelerated demand for vitamin A. The amount in the decreased food intake, plus vitamin A mobilized from the liver, cannot meet the demand. The latter mobilization may not start until the blood level has dropped to a critical level. Our data on the plasma level with and without fever are not conclusive, but they do show a slight drop of the average plasma level with fever. This drop was augmented by inclusion of the 25 per cent with fever who had tuberculosis.

The table of percentage distribution of observations with vitamin A and each of the other tests has been omitted, as nothing significant was apparent that is not evident in tables 2 and 3.

Proteins: Protein nutrition in our population is next in importance in the list of deficiencies. Total protein determinations on the serum are not as helpful in studies of tuberculosis as in other diseases, because the globulin content of the serum rises abruptly with the onset of the disease and masks any decrease in the albumin content of the serum. The albumin-globulin ratio shows this relationship, but is not of much help in our study, for once we know the ratio is changed the actual values of albumin are needed to portray the protein nutrition. When

these figures are examined (table 2) it is evident that the albumin level drops suddenly in the far advanced cases. Apparently the dietary intake of protein substances has not been sufficient to meet the increased demands by the body. Malfunction of the liver has not been proved a factor in the low serum albumin concentrations found in far advanced tuberculosis. The rôle that protein nutrition plays in the resistance to tuberculosis is not established. Attention has been drawn repeatedly to a relation between hypoproteinaemia and lowered resistance to infection. Cannon (23) found at least a partial explanation in the impaired capacity of animals to produce antibodies after their protein reserves had been depleted by artificial means.

Carotene: The functions of carotene in the plasma have not been fully explored. No functions have been described other than as source material for vitamin A. Its blood level is generally agreed to reflect the intake of the foods containing it. The data show a drop in the plasma level in the advanced stage of tuberculosis. This could well be due to decreased intake in these subjects. Carotene conversion is not an instantaneous thing. We have observed many subjects with normal carotene levels and poor vitamin A levels. We have no evidence to date that carotene conversion is impaired in the tuberculous. It is slow even in the normal (20).

Sedimentation rate: Plasma ascorbic acid and sedimentation rate have been linked together by almost every one working in the field. In an earlier publication we stated that our findings, based on the total sedimentation in one hour, did not show a correlation with the plasma level of ascorbic acid (1). This was at variance with the data obtained by Heise (24). The present data, using the maximum sedimentation in five minutes, show a correlation, and the total sedimentation in one hour on the same blood specimen does not correlate with plasma ascorbic acid. Table 4 gives the extent of malnutrition in each sedimentation test group. All the findings show the percentage of observations that are below normal increases as the sedimentation rate does. This does not mean that the various nutrients have profound effects upon each other, but rather that all show abnormal findings when affected by another factor, which is either dietary intake or effect of disease. We do not believe this to be true for serum albumin and sedimentation rate. Gray and Mitchell (25) have reported that serum albumin added to blood with a rapid sedimentation rate slows up the sedimentation. This suggests that there is an intimate relationship between serum albumin and sedimentation rate. This does not rule out similar associations with fibrinogen or alpha and beta globulins (25). The sedimentation rate may be a resultant of the effects of the three proteins and not influenced by the other fluid blood constituents. The albumin appears to be the slowing agent; it is present in the greatest amount. The alpha and beta globulins and fibrinogen, which are present in smaller amounts, appear to have a tendency to increase the rate. Thus, factors influencing the sedimentation test have been identified and the test has new significance in nutrition work. One would expect all persons with a low serum albumin to have an increased sedimentation rate. Our data furnished no exceptions.

Age: It was not surprising to note that calcium, phosphorus and phosphatase

TABLE 4

Percentage distribution according to test group and sedimentation rate

TEST GROUP	SEDIMENTATION RATE—MAXIMUM IN A 5-MINUTE PERIOD			
	1 mm. (324)	2–4 mm. (128)	5–9 mm. (35)	10+ mm. (9)
Ascorbic acid:				
1.0 mg. per cent and up	7%	5%	3%	0%
0.5–1.0	17	13	6	0
Below 0.5	76	82	91	100
Albumin:				
4.5 g. per cent and up	57%	30%	6%	0%
4.0–4.5	33	25	25	11
Below 4.0	10	44	69	89
Globulin:				
3.0 g. per cent and up	20%	63%	84%	89%
2.5–2.9	44	25	13	11
1.8–2.4	25	12	3	0
Below 1.8	1	0	0	0
Albumin-globulin:				
1.65 and up	50%	25%	3%	0%
1.3–1.65	39	38	31	11
Below 1.3	11	37	66	89
Vitamin A:				
110 I.U. and up	39%	24%	12%	0%
85–110	33	28	12	0
Below 85	28	48	76	100
Carotene:				
0.11 mg. per cent and up	68%	48%	32%	0%
Below 0.11	32	52	68	100
Phosphatase:				
2.75 mg. per cent and up	27%	44%	50%	22%
1.5–2.75	63	52	41	56
Below 1.5	10	4	9	22
Haemoglobin:				
15.4 g. per cent and up	45%	20%	6%	0%
12.4–15.4	53	74	76	67
Below 12.4	2	6	18	33
Diagnosis:				
Nontuberculous	66%	35%	26%	0%
Active minimal	6	11	15	0
Active far advanced	1*	9*	21*	56*

* Percentages do not add to 100 as not all diagnosis groups are included.

did not show correlation with age, as they did not vary appreciably in any analysis of the data, but the negative correlation with haemoglobin was unexpected.

TABLE 5

Per cent distribution according to test group and blood haemoglobin

TEST GROUP	BLOOD HAEMOGLOBIN IN GRAMS PER 100 ML.		
	5.4 and plus (169)	12.4 to 15.4 (293)	Below 12.4 (28)
Vitamin C:			
1.0 mg. per cent and up	9%	4%	4%
0.5–1.0	24	12	4
Below 0.5	67	84	92
Vitamin A:			
110 I.U. and up	44%	28%	4%
85–110	32	28	18
Below 85	24	44	78
Carotene:			
0.11 mg. per cent and up	70%	59%	25%
Below 0.11	30	41	75
Albumin:			
4.5 g. per cent and up	63%	35%	29%
4.0–4.5	30	42	11
Below 4.0	7	23	61
Albumin-globulin ratio:			
1.65 and up	49%	34%	25%
1.3–1.65	36	40	14
Below 1.3	15	26	61
Phosphatase:			
Below 1.5 mg. per cent	15%	6%	4%
1.5–2.75	57	59	70
2.75 and up	28	35	25
Per cent standard weight:			
110 per cent and up	16%	9%	7%
90–110	60	60	32
Below 90	24	31	61
Diagnosis:			
Nontuberculous	57%	53%	18%
Active minimal	7	12	18
Active far advanced	2*	4*	36*

* Percentages do not add to 100 as not all diagnosis groups are included.

Perhaps if the age span was extended another thirty years, the slight progressive drop in the percentage of normal observations would prove statistically signifi-

TABLE 6

Per cent distribution according to test group and age

TEST GROUP	AGE IN YEARS		
	20–29 (192)	30–39 (186)	40–49 (112)
Sedimentation rate:			
1 mm	78%	60%	55%
2–4	16	28	35
5–9	4	10	8
10 and plus	2	2	2
Ascorbic acid:			
1.0 mg. per cent and up	7%	5%	4%
0.5–1.0	20	16	6
Below 0.5	73	79	90
Vitamin A:			
110 I.U. per 100 cc. plasma	28%	37%	31%
85–110	35	22	33
Below 85	37	41	36
Carotene:			
0.11 mg. per cent	63%	59%	49%
Below 0.11	37	41	51
Albumin-globulin ratio:			
1.65 and up	48%	33%	31%
1.3–1.65	37	38	40
Below 1.3	15	29	29
Phosphatase:			
Below 1.5 mg. per cent	10%	10%	6%
1.5–2.75	61	60	58
2.75 and up	28	30	36
Haemoglobin:			
15.4 g. per cent and up	39%	34%	31%
12.4–15.4	55	60	64
Below 12.4	6	6	5
Diagnosis:			
Nontuberculous	68%	57%	62%
Active minimal	6	8	5
Active moderately advanced	6	5	9
Active far advanced	3*	6*	7*

* Percentage does not add to 100 as not all diagnosis groups are included.

cant, and possibly the mineral elements would then show more variability and show positive correlations. No attempt to explain why the nutritive status deteriorates with increasing age can be satisfactory because of our limited knowl-

edge. Decreased dietary intake or decreased intestinal absorption could explain it. There is more tuberculosis in the highest age group (table 6), but the slight difference is not enough to explain the drop in the average nutritive status The last three lines of table 6 added give the total percentage of the observations that were made on tuberculous subjects with active disease. This progresses from 15 to 19 and then 21 per cent in the oldest age group, which is in keeping with our knowledge of the age incidence of tuberculosis in males. Only 24 per cent of the tuberculous in the oldest age group had minimal disease, while in about 40 per cent of the younger groups the disease was minimal.

The figures for vitamin A in the age correlation study defy explanation. The age group thirty to thirty-nine has the highest per cent of normal observations; concomitantly the percentage in the next lower age group is decreased. The number of observations is reasonably large, so it should not be an error in sampling. We can offer no explanation and doubt if it is significant.

Other discussion: The data on per cent standard weight probably reflect quantity of food consumed. Study shows that overweight subjects are better nourished in a number of respects than those who are of normal weight. Those that overeat (calories) obtain more of their most needed food constituents. This was especially noticeable with haemoglobin, vitamin A, carotene, ascorbic acid, albumin-globulin ratio and serum calcium. This apparent tendency of the overweight group to be better nourished is enhanced because there were only 2 cases of active tuberculosis to pull down the average in the overweight group. The paucity of tuberculous cases in the overweight group is not sufficient to explain all of the differences in the nutritive status from that of the normal weight group.

Phosphorus, phosphatase and calcium are outstanding in that the population tested showed only a small number of abnormal observations in these items. The body stores or the intakes or both must be adequate according to our present knowledge of these nutrients. Serum calcium is lowered in the far advanced tuberculous cases, but was normal in the minimal and moderately advanced cases.

CONCLUSIONS

1. Adult males with active pulmonary tuberculosis were deficient in ascorbic acid, vitamin A, haemoglobin and serum albumin in the order listed.

2. All nutritional deficiencies were more extensive and profound in tuberculous than nontuberculous subjects. Subjects with far advanced tuberculosis were especially deficient in ascorbic acid, serum albumin, haemoglobin, vitamin A, carotene and serum calcium and in the order listed.

3. Nontuberculous adult males from the same population group were deficient in ascorbic acid, haemoglobin, vitamin A and serum albumin, but to a lesser degree.

4. Persons with arrested tuberculosis had nutritive levels essentially the same as nontuberculous males.

5. There was more active tuberculosis in the oldest age group (forty to forty-nine years), and less of it was in the minimal stage than was found in the younger age groups.

6. Age and haemoglobin showed a negative correlation; the haemoglobin level remained constant as the age advanced.

7. Tuberculous and nontuberculous subjects alike had normal plasma levels of carotene in the presence of abnormally low vitamin A levels, a fact indicating that carotene conversion was inadequate.

8. Plasma ascorbic acid level showed a positive correlation with the erythrocyte sedimentation test when the maximum five-minute drop was used, but no correlation was observed when the total sedimentation in one hour was used.

9. The erythrocyte sedimentation rate showed a positive correlation with the serum albumin concentrations. This fact is believed to give the sedimentation test new significance.

CONCLUSIONES

1. Los varones adultos que padecían de tuberculosis pulmonar activa mostraron deficiencia de ácido ascórbico, vitamina A, hemoglobina y sero-albúmina en el orden enumerado.

2. Todas las deficiencias nutritivas fueron más extensas y profundas en los sujetos tuberculosos que en los no tuberculosos, mostrando los enfermos con tuberculosis muy avanzada, en particular, deficiencia en ácido ascórbico, sero-albúmina, hemoglobina, vitamina A, carotina y calcio sérico en el orden enumerado.

3. Los varones adultos no tuberculosos del mismo grupo de población se mostraron también deficientes, pero no tanto, en ácido ascórbico, hemoglobina, vitamina A, y sero-albúmina.

4. Las personas con tuberculosis estacionada mostraron cifras nutritivas en el fondo idénticas a las de los varones no tuberculosos.

5. Mostró más tuberculosis activa el grupo de mayor edad (40–49 años) y menos en la fase mínima que la revelada en los grupos más jóvenes.

6. La edad y la hemoglobina revelaron una correlación negativa; el tenor de hemoglobina permaneció constante a medida que avanzaba la edad.

7. Los tuberculosos y no tuberculosos mostraron por igual cifras normales de carotina en el plasma en presencia de títulos anormalmente bajos de vitamina A, lo cual indica que era inadecuada la conversión de la carotina.

8. El título de ácido ascórbico en el plasma reveló una correlación positiva con la prueba de sedimentación de los eritrocitos cuando se utilizaba la gota máxima de 5 minutos, pero no cuando se empleó la sedimentación total de una hora.

9. El índice de sedimentación de eritrocitos reveló una correlación positiva con las concentraciones de sero-albúmina, lo cual parece dotar de nueva importancia a la prueba de la eritrosedimentación.

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EPIDEMIOLOGY OF REINOCULATION TUBERCULOSIS

The Epidemiological Importance of the Course of Bacilli and the Route of Invasion in the Reinoculation Types of Pulmonary Tuberculosis

F. M. POTTENGER[1]

In the fight against tuberculosis we have now come to the place where accurate knowledge is more necessary than ever before. The gross measures for prevention which were adopted when every seventh man was dying of the disease were those which were evident to even the casual student, so they were early inaugurated; but the the degree of importance to be ascribed to individual factors now, when the death rate is less than one-fourth as great, is not so clear. However, the knowledge and experience gained in the past sixty years should aid us in determining where greatest stress should be laid.

The intensive study of specific resistance has furnished much valuable information which is necessary to the understanding of tuberculosis, information which may now be used in formulating a more efficient program for its prevention and cure.

To obtain a clear idea of tuberculosis we must understand that the histologic tissue reactions in the foci of disease are partly the specific phenomena associated with the body's protection against bacilli—the complete mechanism being a combination of cellular and humoral elements. The more we study the immunity reaction the better will we understand the various phases of tuberculosis —primary infection and reinoculation, with their varying pathological and immunological reactions; clinical tuberculosis with its varying disturbances in the patient's physiological reactions; and the curative and hostile factors which determine the outcome of the disease.

Physicians have too generally accepted incomplete knowledge of the route of invasion and the source of bacilli of reinfection as though it were final. It is necessary to remember that once infected the host thereafter lives in varying degrees of equilibrium with the bacilli lying within his tissues.

If it were possible to clarify our ideas regarding the action and degree of competency and permanency of the various phases of specific resistance (immunity), we would be on advanced ground for solving the problems associated with reinoculation; for, upon our opinion of this phase of the subject will we base or modify our belief in the relative importance of endogenous and exogenous sources of reinfection; and, accordingly, will we determine what we deem to be the best program for preventing clinical tuberculosis.

FIRST INFECTION VERSUS DISEASE

The source of the bacilli which cause primary infection is nearly always some other human-being who is suffering from open tuberculosis. We still must recognize the possibility of some infection coming from tuberculous cattle but

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in this country the amount is a small and diminishing one. On the other hand, no matter how desirable it is to know, we cannot say with certainty how often the bacilli of reinoculation are from an exogenous and how often from an endogenous source; while bacilli may infect the environment in which many people live, living bacilli may also lie for years in the body of an infected host, in an inactive state, nevertheless capable of taking on activity when the tissues in which they are embedded become favorable to their multiplication and growth. An incompletely healed clinical disease is apt to show repeated reactivations. Even well encapsulated bacilli may now and then become temporarily or continuously active.

During the time between Koch's announcement of the difference in the tissue reactions of a primary infection and a reinoculation, upon which he based the specific therapeutic and diagnostic value of subcutaneous injections of tuberculin, and the discovery of the various local tuberculin tests and the effect of the primary complex upon further implantation of bacilli, much thought was given by clinicians and much experimentation was carried on in laboratories for the purpose of gaining information which would aid in devising effective measures against the disease. Some of this work was erroneous because it was based on the belief that all tuberculosis is of clinical importance.

During this period it was not known that primary infection may take place years before disease is established and that it may be the only evidence of tuberculosis that an individual may ever show. Nor was it known that primary infection is benign, especially in children, and usually limited to the point of implantation and the lymph nodes draining the area, while clinical tuberculosis is a spreading infection due to a series of reinoculations. Yet, when the evidence came to be examined, it could clearly be seen in animal experimentation that first infection changes the tissues and makes them more resistant and causes the defense reaction of the host to be more energetic. There seems to be no satisfactory explanation for the suggestion that what is supposed to be primary inoculation in the adult may frequently extend at once and become a clinical disease. Why should it differ from primary infection in childhood?

After establishing the fact of the cutaneous reaction it was soon learned that those harboring a primary focus in any phase from an infection of a few weeks' standing to a lesion which had undergone calcification may have the reaction of their cells so changed that any of their tissues when again contacted by bacilli —dead or living— or tuberculin, may respond with inflammation. This discovery was unexpected. It was revolutionary. It called for explanation. Koch's experiments had provided the basis for an explanation, but students of tuberculosis had failed to recognize it. After we had the facts which proved that all who are infected do not have active disease, we were soon to find out by the presence of calcified and partially calcified primary nodes that many individuals suffering from clinical tuberculosis had previously had a primary infection which had modified the course of later inoculations, causing them to assume inflammatory characteristics and aspects of chronicity. The same chronicity was found in case of reinoculation in animal experimentation.

HOW MANY BACILLI WILL INFECT?

Speculation has been engaged in as to how many bacilli are necessary to cause infection. This query is of epidemiological as well as academic interest, but cannot be answered with accuracy. It naturally must vary under different circumstances. Krause was probably correct in stating that one bacillus advantageously placed under extra favorable conditions might infect. But it is probable that such extra favorable conditions are rarely, if ever, present in natural infection.

J. E. Pottenger infected 40 per cent of a group of guinea pigs by 3 ± bacilli isolated from cases of active tuberculosis injected intraperitoneally.

But there is a vast difference between experimental and natural infection, and between infection in a guinea pig and man. In natural infection bacilli which are discharged from the body of one tuberculous patient are injured in various degrees by environmental forces before they enter the tissues of a new host. Then, too, they are not placed directly in the tissues but must run the gauntlet of all the physical, chemical and physiological forces which naturally protect the host from invasion. Furthermore, the guinea pig is known to be very susceptible to tuberculosis. That man's natural protective forces are fairly competent to protect him may be judged by the fact that in past centuries when the bacillus was unknown and no precautions were taken, and when in the environment occupied by tuberculous patients conditions favoring infection were always present, the mortality rate of tuberculosis was fairly constant and even began to decline with improvement in the lot of the workers long before specific precautionary measures were taken. No better assurance can be had that most bacilli which are discharged by patients are destroyed either before or after entering the host; for usually they fail to cause disease. With our present program of earlier diagnosis, isolation of the patient, hygienic care and sanitary disposal of sputum, the chances of bacilli in adequate numbers entering the body from an exogenous source and finding lodgment in the tissues under conditions favorable to growth and multiplication are undoubtedly infinitely smaller than in the past—and these ever diminishing. This should encourage us but not cause us to relax in our precautionary measures. The fact that our program renders the environment in which children live comparatively free from bacilli is shown by the fact that less than one-third of school children now are infected as determined by the tuberculin test, while forty years ago nearly all reacted.

What would be a sufficient number of bacilli to cause primary infection probably would rarely be sufficient to infect an immune host. As proof of the fact that the tissues of an immune host resist bacillary invasion it is only necessary to cite the fact that in far advanced tuberculosis millions of bacilli may pass over the bronchial mucous membranes daily for long periods of time not only without implantation taking place but with healing of the lesion occurring. As the total amount of tuberculosis in the population is now decreasing and the association of the people with the disease is becoming less intimate, and the degree of racial resistance which now exerts a protective influence upon civilized

peoples lessens, susceptibility to infection may increase, thus overcoming some of the advantage gained by reducing the numbers of bacilli in the environment. Then primary infection may become common in adults. It will be interesting to see if it will follow a benign course.

While we may not know the number of bacilli necessary to cause either a primary infection or a reinoculation, it is in accordance with our knowledge that larger numbers of bacilli, or more virulent bacilli, or conditions more favorable to the bacilli must be present for reinfection than for a primary infection. The importance of this from the epidemiological standpoint will readily be appreciated.

Regardless of the specific protection that may be established by previous infection, it is important to remember that both primary infection and each reinoculation establish foci within the body from which bacilli may spread to cause new metastases. This possibility exists even though the lesions become apparently healed.

ROUTE OF INVASION

The source of the bacilli and the route of invasion are of prime importance in epidemiology. The aerogenous route presupposes that bacilli enter the body via the air passages through droplets of sputum or dust; and, entering with the currents of air, pass directly into the lungs. The fact that the lung is the chief organ affected is given in support of this theory. But this is not conclusive, for, if this is the chief manner in which infection occurs, it is necessary to assume that bacilli enter the pulmonary tissues more or less readily and that they may localize anywhere that they make contact. This might be true in primary invasion and not in reinoculation.

To establish the aerogenous route in primary infection it is necessary to explain how the focus may be situated in any part of the lung with probably a slight preponderance in the upper half, while the more forceful currents of air enter the lower portions of the lung; and, in reinoculation, how the apical and subapical areas are usually involved when localization in these areas is directly opposed by the intrabronchial forces.

To establish first infection through the nasopharyngeal and gastrointestinal route, on the other hand, it must be shown how bacilli so entering may find their way to the pulmonary tissues. Adherents to this theory point out that bacilli which enter the nasal or oral passages in droplets of sputum, or as dust, immediately come in contact with the moist surfaces of the nasal and pharyngeal mucous membranes and that the natural course would be for them to be precipitated upon the surfaces and either pass directly through the walls into lymph spaces or be swallowed. The mechanism of digestion might be one of great protection to the individual.

Infection through the mucous membrane of the nasopharynx was not uncommonly seen as apparently a primary infection in children whose cervical lymph nodes so frequently suppurated in the days when the environment of tuberculous patients was grossly contaminated and when infected milk was commonly used.

Even to-day tonsils and lymph nodes may frequently show mild infection if examined microscopically. The rationale for diagnostic gastric lavage is based on the tendency to swallow sputum in case the quantity is small. Bacilli entering the digestive tract, whether with food or from soiled fingers and utensils, in case they escape the protective action of digestion, may be absorbed along with fats by the lacteals and reach the lung through the thoracic duct, the venous system, the right heart and the branches of the pulmonary artery. When entering through the nasopharyngeal walls, particularly in first infection, they may either be detained in local lymph nodes or pass through these barriers and enter the lungs by the lymph stream and venous blood, and be screened out in any portion of the lung, but especially where the vessels are narrowed.

What we believe regarding the source and route of the bacilli of reinoculation is another thing. It must be modified by our opinion of the degree of specific protection which is aroused in the host by previous infection and the influence which other factors, particularly those of a mechanical nature, may have upon implantation. That bacilli frequently escape into the blood stream from established foci in an immune host and provide the conditions necessary for metastatic invasion is generally recognized.

Certain mechanical factors favor implantation, especially in case of reinoculation. Of these, flattening of the apices as compared with the middle and lower portions of the lung, the direction of the air current and the difference in respiratory movement must be considered. At birth the upper ribs are horizontal and the chest is barrel-shaped, but when the child has assumed the erect posture, after about the third year of age, the sternum and anterior end of the ribs sink downward, compressing and flattening the apices anteroposteriorly, lessening the respiratory movement compressing the tissues and narrowing the lymph spaces and blood vessels. This brings about conditions which facilitate the lodgment of bacilli which may course in the blood stream in these parts. While it is probable that most bacilli which enter the blood stream of an immune host are destroyed by humoral forces, those which resist destruction, and especially clumps of bacilli, might be easily detained in narrowed vessels, especially if assisted by a local inflammatory reaction caused by their contact with hypersensitive cells.

DISCUSSION

My conception of clinical tuberculosis is that it is a disease accompanied by repeated episodes of metastasis and body reaction, each of which, theoretically, according to its relative severity, strengthens or weakens the host's resistance. New infection is prevented or accomplished, and the patient cures or kills himself, according to the sum total of the effects of the multiple invasions.

While it is accepted that bacilli causing reinoculations may come either from without or from within, too many are inclined to base the measures for prevention on the assumption that they come from without and in point of time gain entrance shortly before the disease is discovered. In my experience in history-taking I find that comparatively few patients give a history of known contact

with open cases of tuberculosis, either immediately or even remotely, prior to developing active disease. However, a large percentage give evidence of previous infection either in the form of Ghon's nodes, a history of reaction to tuberculin, or some limited form of the disease, such as perirectal abscess, pleurisy or a mild pulmonary lesion which had shown limited tendency to extend. Any one of these foci could furnish the bacilli for metastatic spread.

Regardless of some degree of immunity being present this increased protection might be negatived or at least partially overcome by the more favorable position of the bacilli of reinfection when coming from foci already established within the body. Metastases may take place by bacilli passing from existing foci into contiguous tissue, by being transmitted through the blood and lymph streams or via the natural channels.

The important question to be answered is, how can viable bacilli lying within the tissues become mobilized and how frequently does this occur? That this can occur may be stated unequivocally. How often it occurs we do not know but the conditions for spread may appear at any time as long as viable bacilli are present in the tissues. We (1) have observed many patients for years after discharge from the sanatorium, examining their sputum at intervals using a sensitive technique, and it is surprising to find that ex-patients may be clinically well, showing no demonstrable signs of disease and capable of carrying on their usual work, and still now and then discharge small numbers of bacilli into the bronchi, and probably also into the blood stream had we efficient methods for detecting them. Doubtless this same thing occurs in patients who give a history of having overcome an active disease in the past; also in many who had active lesions without knowledge of their presence. Under extraordinary circumstances we find reactivation in individuals who have recovered from an active disease ten, twenty and thirty years before, and who have lived normal lives in the meantime.

The fact that foci are already within the body and not infrequently within the walls of blood vessels from which they may readily pass into the lumen, and in the pulmonary tissues from which they may readily escape into the air spaces and bronchi when the focal architecture is disturbed from any cause, makes endogenous reinoculation comparatively simple. Endogenous invasion may be precipitated by any factor which will cause increased permeability of the perifocal tissues. This may be caused by other respiratory infections such as measles, whooping-cough, influenza and bronchitis. Diabetes, silicosis and substances irritating to the foci may be responsible for mobilizing bacilli and producing spread, particularly if conditions favorable to the parasite are present. In this, malnutrition, overwork and any prolonged strain producing chronic impairment of health may be readily accepted as disturbing factors. Sudden and marked weather and seasonal changes may do the same by calling out a marked stimulation in and around foci of infection as evidenced by the increase in numbers of cases of active tuberculosis and deaths which occur in the spring and fall as compared with other seasons of the year.

It seems reasonable to assume that the mild proliferative lesions which are so often found at or near the apex of the lung of patients who have previously had a

primary infection in some portion of the body might easily have been established by bacilli, comparatively few in numbers, entering the blood stream from existing foci, escaping the protective forces of the blood, and meeting in the apical tissues conditions usually favorable to their local detention.

Considering these various factors we might with profit reëxamine the premises on which we are basing our present conception of both the route of invasion and the source of bacilli of reinvasion. One hesitates to disturb accepted ideas but, at times, progress can be made only by so doing.

In making plans for the final assault against tuberculosis, these simple problems will loom higher than they have in the past. To establish the exogenous source of reinfection by the aerogenous route, it is necessary to assume that the numbers of invading bacilli are fairly large. Bearing upon the numbers of bacilli contained in droplets which are scattered in coughing, sneezing and talking, it has been shown that only the smaller ones remain suspended in the air for any length of time, while the larger ones, which presumably carry more bacilli, quickly fall to the floor. Moreover, the exogenous source makes it necessary to assume that previous infection establishes either no resistance to the bacilli entering the tissues or an inefficient one; or that reinfection usually takes place when, for some reason, the resistance of the host is low. Then, too, the fact that reinoculation foci are located differently from those of first invasion must be explained. In Ghon's study, the localization of primary single lung foci show no marked predilection for any portion of the lung. On the contrary, early lesions of the reinoculation type are found in the overwhelming majority of instances in the upper part of the lung.

In reinoculations implantation could take place by the haematogenous route whenever the bacilli come from a focus already within the body or from without through the digestive tract. In both instances, except in early life, localization in the superior portions of the lung is favored by the relatively compressed apical tissues. In both instances, too, the likelihood of bacilli causing new foci is undoubtedly reduced and often overcome by the heightened protective forces of the body called into action by previous infection. Doubtless there are many instances of bacilli attempting invasion to each infection which occurs.

To account for reinoculation of the apical areas by the aerogenous route, the resistance of the tissues to invasion must be taken into account; and whereas compression of the tissues, especially the vessels, might favor haematogenous spread, compression of the air-passages might interfere with bacilli reaching these areas through the bronchi. At least the bacilli should not show a predilection for the apices for the direction of the main current is toward the bases. This fact is cited as an explanation of the difference in localization of pneumonia and tuberculosis. Even the newly studied virus pneumonias seem to show a preference for the nonapical portions of the lung. But we must not lose sight of the fact that the bacilli of aerogenous origin would escape the hostile immune factors in the blood stream and be opposed only by those of the tissues themselves, so smaller numbers of bacilli entering the air passages might be capacle of establishing new foci.

That man does not readily develop clinical tuberculosis on contact, no matter by what route the bacilli enter, is proved, as previously mentioned, by the history of the past. But that he lives during a great proportion of his life in a biological equilibrium with bacilli in his tissues is also evident. This must be evident from the aforementioned facts that with millions of people suffering from active tuberculosis throughout the ages and often living in closed rooms, shunning the open air and sunshine and expectorating promiscuously, the morbidity and mortality remained fairly stable; and that, when the tuberculin test was first put into general use in large groups of the population, it was shown that nearly all people in the cities, and a somewhat smaller number in the country, were infected by the time they attained the age of fifteen years; yet, the proportion which developed active disease was relatively small. Throughout the ages and until recently, the amount of disease among the people remained about the same —one active case replaced each death. We may therefore justifiably assume that limited early infections have protective value. The active measures taken in the past sixty years, in spite of their inefficiency, have reduced the disease by three-fourths, and infection apparently in greater proportion. This promises well for continued success in our program of prevention; yet, reasoning biologically, we must expect the people to lose part of their immunological protection as the disease becomes less prevalent, and primary infection will probably become more common in adolescent and early adult life.

Whether bacilli enter the lung directly by way of the air passages or indirectly through the nasal and oral mucous membranes and the gastrointestinal canal in causing primary infection is of comparatively little epidemiological consequence, for the source of bacilli is the same in either case; but in the reinoculation type of the disease, to know whether the bacilli are of endogenous or exogenous origin is of the greatest importance.

It is rational to believe that both sources may be responsible for infection, but could it be definitely known that most instances of active disease are due to direct contact with active open cases of tuberculosis, our course would be clear. We should spend most of our effort on isolation of the patient and sanitation. The program which we employ to prevent first infection would be ample to prevent reinoculation.

On the other hand, should the chief or a consequential source of bacilli responsible for reinoculation be the foci which are already within the body, then we should, aside from the precautionary measures used to prevent infection in the environment, exert a further effort to secure healing of every infection and to keep the infected individual in a highly resistant state so that his protective mechanism will afford him greatest protection against his own bacilli. To this end, all measures which improve physiological resistance are applicable and should be especially applied to those who have had tuberculosis of clinical importance. Better hygiene, better nutrition, emotional stability and less physical depression should be especially helpful.

Immunity or specific resistance is a labile mechanism. When active, it undoubtedly is competent to ward off or modify the action of many bacilli.

When lowered or in abeyance, it puts the individual exposed to reinfection in a condition approaching that in which he was prior to first infection.

Most of the tuberculous patients who seek medical aid to-day have had many reinoculations with many resultant foci of varying degrees of severity. This makes our problem difficult, for the best that we clinicians can do in a short course of treatment in such a chronic disease is to secure a truce between the patient and his bacilli, a truce which may be broken on either side: by the bacilli in case their environment at any time becomes congenial for their growth and multiplication; by the patient in case he can increase his resistance sufficiently, maintain it continuously at a high level, and thus prevent the bacilli from producing further activity.

Here is where we are making one of our most abject failures in treating tuberculosis. Both physicians and patients are prone to lose interest; or, for other reasons, treatment is often interrupted before healing has been attained. By relaxing measures necessary to complete healing, the patient's defensive powers are allowed to lower, the tissues lose their resistance and new activity starts. Thus are caused the many relapses which plague us and make us almost lose confidence in therapeutic measures. A little longer treatment and a great deal longer extension of the careful life after treatment has been finished, and a full rehabilitation of the patient before he is discharged from observation, and many of the reactivations which we speak of as "breakdowns" would be avoided and many sources of infection would be permanently instead of temporarily elminated.

SUMMARY

1. Now that the morbidity and mortality of tuberculosis are rapidly declining, accuracy in our information regarding infection becomes ever more important.

2. Bacilli entering the tissues for the first time are opposed only by the body's natural physiological defense reactions. Bacilli of reinoculation are opposed not only by these normal processes but by an exaggerated physiological mechanism which we recognize as specific defense or immunity. This is an important fact epidemiologically because it makes reinfection more difficult and the resultant disease more chronic.

3. Our methods of prevention are based upon our opinion as to how the lung becomes infected—the source of the bacilli and the route by which they reach their destination. While bacilli responsible for primary infection must come from an exogenous source, it is not so certain that bacilli causing reinoculation are of the same source. Metastases of endogenous origin seem to be a reasonable explanation of most of the disease that we meet clinically.

4. If the chief source of bacilli responsible for reinoculation is exogenous, then our protective measures must be directed mainly toward preventing the scattering of bacilli in the patient's environment, the same as in case of primary infection. If, on the other hand, the chief source, or any great amount of reinoculation is of endogenous origin, we should not only direct our attention to bacilli which are discharged by patients, but also or even more to the bacilli lying within

the tissues of the individual who has been infected; because so long as there are viable bacilli in the tissues there is a possibility of their reactivation and forming new metastases.

5. The endogenous source of reinoculation calls for more thorough treatment, rehabilitation and more adequate after-care of the tuberculous patient.

SUMARIO

1. Hoy día en que van en rápido descenso la morbidad y la mortalidad de la tuberculosis, se vuelve más importante que nunca contar con datos exactos acerca de la infección.

2. Los bacilos que penetran por primera vez en los tejidos son resistidos únicamente por las reacciones de defensa fisiológica naturales del organismo. Cuando tiene lugar la reinoculación, los bacilos son combatidos no tan sólo por esos procesos normales sino por un mecanismo fisiológico exagerado al que damos el nombre de defensa específica o inmunidad, lo cual constituye un punto importante desde el punto de vista de la epidemiología dado que dificulta más la reinfección y convierte en más crónica la lesión resultante.

3. Nuestros métodos profilácticos están basados en nuestra opinión en cuanto a la manera en que se infecta el pulmón: la procedencia de los bacilos y la vía por la cual llegan a su destino. Aún los bacilos causantes de la infección primaria deben reconocer una procedencia exógena; no es tan seguro que procedan del mismo foco los que ocasionan la reinoculación Las metástasis endógenas parecen ofrecer una explicación lógica de la mayor parte de la enfermedad clínica que encontramos.

4. Si el principal foco de bacilos causantes de la reinoculación es exógeno debemos entonces encaminar nuestras providencias protectoras, principalmente, en el sentido de impedir la dispersión de bacilos en el medio ambiente del enfermo, lo mismo que hacemos en la infección primaria. En cambio, si el foco principal o una gran proporción de la reinoculación son endógenos, debemos no tan sólo fijar nuestra atención en los bacilos expulsados por los enfermos, sino también y hasta más, en los bacilos que restan en los tejidos del individuo infectado, porque en tanto que haya gérmenes viables en los tejidos es posible que se reactiven y formen nuevas metástasis.

5. El foco endógeno de reinoculación exige un tratamiento más completo, reabilitación y asistencia post-sanatorial mas adecuada del tuberculoso.

REFERENCE

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TUBERCULOUS PNEUMONIA[1]

D. O. SHIELDS[2]

The treatment of tuberculous pneumonia varies greatly in different clinics, but most cases are probably treated according to three major plans of therapy: (*1*) immediate pneumothorax; (*2*) delayed pneumothorax; (*3*) bed-rest until caseated areas have liquefied and then pneumothorax or thoracoplasty to close cavities and control infection.

The reasons given for immediate pneumothorax are control of toxaemia, prevention of spread of caseation by contiguity, conversion of sputum as soon as possible, and obtaining a pleural space before adhesions form. Others feel that the temperature and symptoms of acute tuberculous pneumonia should be partially abated because of the danger of empyema, bronchopleural fistula and interference with the mechanism of raising sputum when pneumothorax is used during the acute stage. Bed-rest is advocated by those who feel that it is useless to try collapse measures on consolidated tuberculous infiltrations and favor waiting until areas of caseation have excavated and the infection is subacute before pneumothorax or thoracoplasty is used. When the area of pneumonic consolidation is extensive or when resistance is poor, as in the Negro race, it is sometimes felt that the prognosis is hopeless and attempts to control the infection by collapse measures would only increase the complications and make the patient more uncomfortable during the terminal stage. That none of the three forms of therapy shows a clear-cut advantage over the others is evidenced by the fact that each method is advocated by physicians of wide experience in tuberculosis. The literature is barren of statistics revealing the results of each method of treatment.

With this in mind, 52 patients with tuberculous pneumonia, entering Grasslands Hospital from 1932 to 1942, were analyzed. Four white patients received bed-rest only and all died. Nine Negro patients were treated with bed-rest, resulting in 8 deaths and one patient with quiescent[3] disease. Sixteen white patients were given pneumothorax, followed by thoracoplasty in 5 cases. The results were 4 deaths, 2 with active disease, 2 quiescent, 2 apparently arrested and 6 apparently cured according to follow-up observations. Twenty-three Negro patients received pneumothorax, followed by thoracoplasty in 3 cases. Seventeen patients are dead, 3 hopeless, 2 quiescent and one apparently arrested.

The patients who received bed-rest only were extremely ill on admission and some died within a few days. In most cases the prognosis was felt to be so poor that collapse treatment was not attempted. For this reason they should not be used as a control series to compare with patients who were given pneumothorax.

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[3] The term quiescent as used throughout this paper refers to cases with a negative sputum that are asymptomatic and may or may not be ambulant. The X-ray films in all cases showed stationary or retrogressing disease. It was felt that the prognosis in all was at least fair. Other terms used are as defined by the National Tuberculosis Association or are self-explanatory.

The patients who received pneumothorax were divided into (*1*) those who had pneumothorax induced within the first forty days after onset, (*2*) within forty-one to eighty days after onset and (*3*) over eighty-one days after onset. From table 1 it can be seen that the percentage of empyemata was greater in the last two groups. The adhesions were graded and the average for each group determined.

TABLE 1

Pneumothorax in tuberculous pneumonia

	0–40 DAYS AFTER ONSET	41–80 DAYS AFTER ONSET	OVER 81 DAYS AFTER ONSET
White 16 cases	6 cases Empyema 2 cases *Adhesions 1.3 Death 1 Quiescent 1 Apparently cured 4	5 cases Empyema 3 cases Adhesions 3 Deaths 2 Active 1 Quiescent 1 Apparently cured 1	5 cases Empyema 4 cases Adhesions 2.2 Death 1 Active 1 Apparently arrested 2 Apparently cured 1
Negro 23 cases	10 cases Empyema 3 cases Adhesions 2.1 Deaths 8 Hopeless 1 Quiescent 1	11 cases Empyema 5 cases Adhesions 2.6 Deaths 7 Death 1 due to abdominal infection Hopeless 2 Active 1	2 cases Empyema 1 case Adhesions 2.5 Death 1 Apparently arrested 1
Total 39 cases	16 cases Empyema 5 cases Adhesions 1.8 Deaths 9 Hopeless 1 Quiescent 2 Apparently cured 4	16 cases Empyema 8 cases Adhesions 2.8 Deaths 10 Hopeless 2 Active 2 Quiescent 1 Apparently cured 1	7 cases Empyema 5 cases Adhesions 2.3 Deaths 2 Active 1 Apparently arrested 3 Apparently cured 1

* Note: Instead of averaging the adhesions it would be preferable to plot a mean but as the cases were so few it was felt that this would be of little value. The adhesions for each group were as follows: 0–40 days, white—2, 2, 2, 0, 2, 0, Negro—1, 4, 1, 2, 4, 0, 4; 41–80 days, white—4, 4, 4, 1, 2, Negro—2, 3, 2, 4, 3, 2, 4, 2, 0, 3, 4; over 80 days, white—1, 2, 3, 3, 2, Negro —3, 2.

For grading of adhesions see footnote following table 2.

In white patients, the cases in which pneumothorax was started forty-one to eighty days after onset seemed to have more extensive adhesions. In Negro patients there was little difference in the three groups. The total, however, showed slightly less extensive adhesions in the group where pneumothorax was started earliest. The mortality in white patients was lower in the first and third groups. In Negro patients the mortality was high in all groups. It should be

TABLE 2

Effect of adhesions

† ADHESIONS	0	1	2	3	4
White 16 cases	2 cases Empyema 0 Apparently arrested 1 Apparently cured 1	2 cases Empyema 1 (14 mos.)* Death 1 Apparently cured 1	7 cases Empyema 4 (8.2 mos.) Death 1 Active 2 Quiescent 1 Apparently cured 3	2 cases Empyema 2 (5 mos.) Death 1 Apparently arrested 1	3 cases Empyema 2 (2 mos.) Death 1 Quiescent 1 Apparently cured 1
Negro 23 cases	3 cases Empyema 0 Deaths 3	3 cases Empyema 2 (2.5 mos.) Deaths 3	6 cases Empyema 4 (6 mos.) Deaths 4 Hopeless 1 Quiescent 1	4 cases Empyema 2 (6 mos.) Deaths 2 Death (abdominal infection) 1 Apparently arrested 1	7 cases Empyema 1 (¾ mo.) Deaths 4 Hopeless 2 Active 1
Total 39 cases	5 cases Empyema 0 Deaths 3 Apparently arrested 1 Apparently cured 1	5 cases Empyema 3 (8 mos.) Deaths 4 Apparently cured 1	13 cases Empyema 8 (10 mos.) Deaths 5 Hopeless 1 Active 2 Quiescent 2 Apparently cured 3	6 cases Empyema 4 (5.5 mos.) Deaths 4 Apparently arrested 2	10 cases Empyema 3 (1.5 mos.) Deaths 5 Hopeless 2 Active 1 Quiescent 1 Apparently cured 1

† Adhesions—0. Free space.

1. Adhesions interfering only slightly with collapse.
2. Adhesions interfering to a moderate degree with collapse.
3. Adhesions interfering so that there is only slight collapse.
4. All of diseased area adherent or wide adhesions allowing little or no collapse.

* Average months empyema developed after pneumothorax started.

remembered that the last group included patients who could be classified as subacute tuberculous pneumonia. In 3 of the 7 cases, pneumothorax was not started until four months after onset. It may be that this group includes some cases with better resistance or less virulent tubercle bacilli than the other groups.

The impression was gained that the extent of the adhesions coincided more closely with the development of empyema than the time after onset at which pneumothorax was started. When the analysis was made with the cases graded from pneumothorax with a free space to grade four adhesions, it was found that those with a free space developed no empyema, while the percentage of empyemata increased slightly with the extent of the adhesions except in the last group. In this group the pneumothorax was often discontinued before empyema had a reasonable chance to develop. In white patients there seemed to be a definite tendency for the empyema to develop earlier with more extensive adhesions.

There was little difference in the mortality in cases that developed empyema and those that did not. Nine white patients developed empyema with the following results: one death, 2 active cases and 6 patients quiescent to apparently cured. Seven white patients without empyema resulted in 3 deaths and 4 cases apparently arrested or apparently cured. In Negro patients, 9 developed empyema and 9 died. Fourteen Negro patients without empyema resulted in 8 deaths, 3 hopeless, one active, one quiescent and one apparently arrested. This makes a total of 18 cases with empyema resulting in 10 deaths, 2 active and 6 quiescent to apparently cured. Twenty-one cases without empyema resulted in 11 deaths, 3 hopeless, one active and 6 quiescent to apparently cured.

Eight thoracoplasties were done with only one death which was due to a subphrenic abscess following a cholecystectomy one year after discharge. One case is hopeless and the other 6 cases are classified: 2 quiescent, 2 apparently arrested and 2 apparently cured. Five patients were white and 3 were Negro. Six of the thoracoplasties were done on patients who had empyema and only 2 on patients without empyema. Because results with thoracoplasty following pneumothorax were good, and as 6 cases receiving thoracoplasty were in the empyema group, it is felt that this may explain the apparent innocuousness of empyema.

Many cases did well with pneumothorax for a considerable period of time and then reactivated. Because of the encouraging results with patients who subsequently received thoracoplasty, all pneumothorax cases in which thoracoplasty was or could have been done were tabulated. The X-ray films, temperatures, weight curves and clinical symptoms of these patients were checked and it is felt that none were poor surgical risks. The cases were divided into groups from apparently cured cases with reëxpanded lungs to those in which the pneumothorax was a therapeutic failure in a few months. Of 19 cases selected, 11 had sputum converted and cavities closed following pneumothorax and were considered therapeutic successes. In 5 of these cases the lungs were voluntarily reexpanded and 2 reactivated on reëxpansion. Three cases reactivated under what was considered a successful pneumothorax, making a total of 5 out of 11 cases that reactivated under pneumothorax or on reëxpansion. Three patients have

reëxpanded lungs and are apparently cured and 3 patients are still returning for pneumothorax refills. There is a chance that some of the latter group may reactivate with reëxpansion. In 4 of the 19 cases the tuberculosis was not controlled after one or two years of pneumothorax. The tuberculosis was not progressive but there was an occasional positive sputum. Thoracoplasty was done in all these cases and all were discharged as apparently arrested. There

TABLE 3

Pneumothorax cases in which thoracoplasty probably could have been done

	PNEUMOTHORAX REËXPANDED—PATIENT APPARENTLY CURED	PNEUMOTHORAX	REACTIVATED ON REEXPANSION	REACTIVATED UNDER PNEUMOTHORAX	UNCONTROLLED WITH PNEUMOTHORAX	PNEUMOTHORAX THERAPEUTIC FAILURE
White 12 cases	3 cases	2 cases Quiescent 1 Apparently cured 1	1 case Thoracoplasty, apparently cured	2 cases 2 active	2 cases 2 thoracoplasties (2 apparently arrested)	2 cases 2 thoracoplasties (1 case quiescent) (1 case apparently cured)
Negro 7 cases	None	1 case quiescent	1 case 1 death	1 case 1 death	2 cases 2 thoracoplasties (2 apparently arrested) (1 died later of abdominal infection)	2 cases (2 cases active)
Total 19 cases	3 cases Apparently cured 3	3 cases Quiescent 2 Apparently cured 1	2 cases 1 death Apparently cured 1	3 cases 1 death 2 active	4 cases (4 thoracoplasties, apparently arrested)	4 cases 2 active 1 thoracoplasty, quiescent 1 thoracoplasty, apparently cured

were 4 cases in which the pneumothorax was considered to be a therapeutic failure after a few months because of extensive adhesions and continued positive sputum. Two of these received thoracoplasty and one is apparently cured according to follow-up studies and the other is quiescent but still in the hospital. It can be seen from the totals that the results with thoracoplasty were slightly better than the group of "therapeutically successful" pneumothorax cases, even though the thoracoplasties were done on a less favorable group.

Because the temperature is considered an important guide in the selection of the optimum time for induction of pneumothorax, an analysis of the temperature before and after pneumothorax was started was attempted. There were 9 white patients who had a temperature of 102°F. or less before pneumothorax was induced. Seven of the 9 developed empyema and the results were as follows: one death, 2 active, 2 quiescent and 4 apparently cured. When the temperature was over 102°F. only 2 of the 7 white patients developed empyema, but results were: 3 deaths, 2 apparently arrested and 2 apparently cured. In Negro patients, 8 had a temperature of 102°F. or less and only 2 developed empyema. Results were: 4 deaths, one active, one quiescent and 2 apparently arrested. Fifteen Negro patients had a temperature over 102°F. and 6 developed empyema. There were 14 deaths and one has active disease.

Following the induction of pneumothorax, 12 patients showed an immediate fall in temperature, 8 a slow fall, 13 no change and 6 cases an increase in temperature. There seemed to be little correlation between the temperature before pneumothorax and its course following induction. For example, 6 of the 12 cases that showed an immediate fall had a temperature of 103°F. or more before pneumothorax, 4 of the 8 having a slow fall had a temperature of 103°F. or more before collapse was started, 8 of the 13 cases with no change had 103°F. or above as did 4 of the 6 cases having an increase following induction. It is difficult to determine if this increase in percentage in the last two groups has significance.

Because a fall in temperature is considered to be a good prognostic sign, all temperature charts were checked to discover cases that had a definite fall in temperature after bed-rest was started and before pneumothorax was induced. Six such cases were found. Three of the 6 had a temperature of 103°F. or more. Two of the patients were white, 4 were Negro and all 6 died. A number of patients had pneumothorax started soon after admission so that there was not sufficient time for the temperature to show a fall before induction.

DISCUSSION

It is realized that nothing of statistical importance can be obtained from the analysis of only 52 cases; however, impressions can be obtained from a small series and may be of some importance.

Because of the belief that cases of tuberculous pneumonia with partial consolidation react differently from those with dense homogeneous consolidation, an attempt was made to classify the cases into partial consolidation (confluent bronchopneumonia) and complete consolidation. This attempt at classification was based on type of onset, fever, degree of toxaemia, physical and laboratory and X-ray findings. Typical cases could be placed in the two groups but there were many borderline cases in which it could not be done accurately and the attempt was abandoned. However, I think it can be stated that typical cases with only partial consolidation responded much better to pneumothorax and in white patients had a lower mortality than the cases with complete consolidation.

In tuberculous pneumonic consolidation it is, of course, difficult to determine how much of the infiltrate is due to true caseation and how much is due to exuda-

tion. Many cases with dense homogeneous consolidation showed no collapse with pneumothorax and in most of the cases excavations appeared and the infection progressed, the pneumothorax appearing to have no effect on the course of the disease. A few of the cases with complete consolidation showed slow collapse, eventual partial clearing and control of the infection under pneumothorax. In the former cases the consolidations were probably mostly true caseation and in the latter the infiltrate was probably largely exudative. I have the impression that extensive caseation is more apt to have a rather high sustained temperature with few râles until liquefaction begins to take place than is the case with a dense homogeneous consolidation which is largely exudative. However, I do not feel that the two can be differentiated with much accuracy.

Cases in which the infiltrate gave the X-ray appearance of dense mottling, with high fever and moderate or severe toxaemia, often developed into a dense homogeneous consolidation with rapid progression of the disease. It is felt that if pneumothorax were induced before complete consolidation had taken place the chances of controlling the infection would be improved. It does not appear from the results in this small group of cases that complications are increased by the early induction of pneumothorax and there is slight evidence that adhesions are less extensive with early induction. Empyema appears to be closely related with the extent of pleural adhesions probably because both represent pleural inflammation. Bronchopleural fistula occurred only once in 39 cases.

The results in Negro patients are discouraging but there were at least 4 cases in which thoracoplasty following pneumothorax would probably have given the patient a fair chance to recover. Results with thoracoplasty (all of which followed pneumothorax) were fairly good. Meltzer (11, 13) and Coryllos and Hochberg (9) have also reported fairly good results with thoracoplasty in caseous pneumonia and acute tuberculosis.

Because of the tendency for tuberculous pneumonia to reactivate either under pneumothorax or on reëxpansion, thoracoplasty should be seriously considered if the lesion is extensive and if there is evidence of considerable caseation.

The temperature may be of more importance as a guide than this series seems to indicate, but I do not think a high fever should necessarily contraindicate the induction of pneumothorax. In certain cases a fever of 102° to 104°F. may be a definite indication to induce pneumothorax, while a similar case with a fever of 99° or 100°F. and slight toxaemia might be carefully observed while receiving strict bed-rest.

SUMMARY

The value of an analysis of a group of cases should be in sharpening clinical impressions and not in setting up a rigid plan of therapy. This is especially true in a small series of cases where chance alone may account for the difference in results. With this in mind, a summary of the therapy that seems to benefit certain cases of tuberculous pneumonia might be attempted.

Immediate pneumothorax appears to produce the best results as compared with bed-rest in cases of partial consolidation with moderately high fever and

moderate or severe toxaemia. There will also be some cases of dense homogeneous consolidation that will slowly respond to pneumothorax. In extensive, complete consolidation collapse will probably not be effective and the progress of the disease not changed by the pneumothorax.

Cases of partial consolidation with a low grade fever and mild symptoms may be watched carefully on strict bed-rest, and pneumothorax induced if extension occurs or symptoms increase. Some of these cases may be treated with primary thoracoplasty if symptoms are mild and it is evident that collapse will be needed to close cavities.

Thoracoplasty should probably follow pneumothorax if there is evidence of inadequate collapse due to adhesions or if the caseation was extensive. It is possible that thoracoplasty would be better tolerated in selected cases of tuberculous pneumonia than is generally supposed.

CONCLUSIONS

According to observations in a group of 52 patients, the following conclusions were reached:

1. Early pneumothorax in tuberculous pneumonia does not increase the percentage of empyemata.
2. Adhesions appear to be slightly less extensive if pneumothorax is induced early.
3. Empyema develops more frequently in cases with extensive adhesions.
4. Thoracoplasty following pneumothorax gives fairly good results.
5. Reactivation in tuberculous pneumonia, both while pneumothorax is being given and following reëxpansion, occurs in a high percentage of cases.
6. There seems to be little correlation between temperature and the development of empyema.
7. Following induction of pneumothorax in 39 patients, 12 showed an immediate fall in temperature, 8 a slow fall, 13 no change and 6 an increase in temperature.

CONCLUSIONES

Por las observaciones realizadas en un grupo de 52 enfermos se alcanzaron las siguientes conclusiones:

1. En la neumonía tuberculosa el neumotórax temprano no acrecienta el porcentaje de empiemas.
2. Si se provoca tempranamente el neumotórax las adherencias parecen ser ligeramente menos extensas.
3. El empiema se presenta más frecuentemente en los casos en que hay adherencias extensas.
4. La toracoplastia consecutiva al neumotórax dió resultados bastante buenos.
5. Tanto mientras se ejecuta el neumotórax como después de la reexpansión, se presenta reactivación en un elevado porcentaje de los casos de neumonía tuberculosa.

6. Al parecer hubo poca correlación entre la temperatura y la aparición de empiema.

7. Después de provocarse neumotórax en 39 enfermos, 12 revelaron una baja inmediata de la temperatura, 8 una baja lenta, 13 no mostraron alteración, y 6 acusaron elevación térmica.

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RECENT ADVANCES IN THE CAMPAIGN AGAINST TUBERCULOSIS[1]

R. G. FERGUSON[2]

In war, as is all too vivid in the memory of every reader, scientific changes wrought by invention in years and even in months render tried and trusted tools obsolete, and may shift effective attack from land to sea, or sea to air. Yet, the fundamental strategy, such as swiftness, surprise, attack and counterattack, has altered little since ancient times.

So in the campaign against that eternal, ubiquitous and infectious enemy, tuberculosis, certain factors are changing rapidly even though fundamental principles of strategy have not altered since the days of Robert Koch.

Science and invention have provided new and better equipment for the discovery and treatment of the disease: the stethoscope, the microscope, culture media, tuberculin, the X-ray, the photofluorograph for discovery; rest from work, bed-rest, temporary lung rest, permanent surgical collapse, and surgical resection for treatment. Nevertheless the fundamental strategy of control and eradication of this obstinate and most adaptable of infectious diseases remains unchanged. This strategy includes: early discovery, segregation of the infectious host and increasing the resistance of the unavoidably exposed persons in every way possible —in other words, the common strategy for the control of all communicable diseases.

Certain important differences exist between tuberculosis and other respiratory diseases which make the former more responsive to isolation. Acute respiratory diseases, almost always accompanied by communicable rhinitis and sore throat, are without exception infectious. On the other hand, in 75 per cent or more of persons who have tuberculosis a small area of lung is affected which resolves without rupturing to the surface and without becoming infectious. Moreover, acute respiratory diseases depend for their spread on the fact that many cases are communicable for a short period, whereas the spread of tuberculosis depends upon a long and much more slowly developing period of infection in a few cases. There is much more time to isolate before the seeds are shed.

The early results of this thesis translated into practice may be set forth briefly:

(*1*) Where, in accordance with an active program, the tuberculous sick are promptly admitted for hospital treatment, and where contacts and ex-patients are followed, the so-called well public includes only a small residuum of unknown spreaders. In Saskatchewan, with a tuberculosis death rate of approximately 20 per 100,000 non-Indian population, the unknown spreaders found in all age groups numbered one per 1,000. Under a similar program the unknown spreaders might be expected to vary with the death rate. This finding is significant; where

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the death rate is low and the program active, the incidence of unknown infectors is very low.

(*2*) Where active segregation for treatment has been practiced over a long period, the incidence of infection decreases rapidly. Examination of the Normal School pupils in Saskatchewan indicated that positive reactors, as measured by the tuberculin test, had fallen from 75 per cent in 1921 to 15 per cent in 1941.

This experience would be less convincing if it did not pertain to urban centres. In the city of Saskatoon tuberculin testing of a cross section of school children has shown that the reactors dropped from 53 per cent in 1921 to 14 per cent in 1934. The evidence among Saskatoon preschool children, derived from tuberculin testing new school entrants, indicates that in 1936 among 348 entrants 3.2 per cent were positive to tuberculin, while in 1942 only one positive reactor was found among 340 entrants, or less than one-third of one per cent. This evidence tends to show that tuberculosis may be reduced to a minor cause of death by the elimination of infection.

(*3*) Segregation of patients for treatment is the method proved to be most effective in the elimination of infection. An adequate number of beds for treatment is still the greatest need in the campaign against tuberculosis in Canada. Several provinces are short of beds to segregate and treat patients recently discovered among civilians. Then, too, the time is approaching when the Army will be demobilized. Health authorities have the experience of the last war as a warning, and they have had plenty of time for preparation. Accommodation should be provided now for casualties resulting from tuberculosis among the armed forces.

(*4*) With reference to the unavoidably exposed, the protection against tuberculosis of nurses and other employees in general hospitals, mental hospitals and sanatoria is a responsibility that rests upon all health workers and particularly on tuberculosis workers. This problem was increasing in Saskatchewan until recently, notwithstanding new and improved nurses' homes, better food, supervision by dietitians, and better training in the technique of communicable disease.

Since March, 1938, 1,800 nurses in training, as well as exposed hospital and sanatorium employees in Saskatchewan, have been vaccinated with BCG; in all, only 10 persons so vaccinated have developed lesions. A provisional report on five years' experience with prophylactic vaccination will be made in 1944.

(*5*) The spread of tuberculosis depends upon the fact that a few cases are infectious for a long period. Where a selective case-finding program has already been established, the problem lies in an economic method for the discovery of the unknown spreaders. Until recently this problem has defied solution. The invention of the photofluorographic film has provided a means whereby miniature films can be made available in mass surveys at a cost of fifteen to twenty cents per person, including the salary of physicians and a technical staff; that is, a cost of $20,000 for the examination of 100,000 people. These films are satisfactory for the selection of definite tuberculous cases. Persons so selected can be further investigated clinically and radiologically.

The cheapness of this method of discovering unknown spreaders removes at

last the financial barrier to case-finding, and opens the way for a great advance in the eradication of tuberculosis. No city or municipality is so small or large that it cannot raise the cost of such a survey.

The active phase of tuberculosis prevention is now at hand. In the process of reducing infection in a community or province, a stage is reached when it is opportune to alter the objective of the attack from a tuberculosis *control* program to an *eradication* program. A province or state can conduct mass case-finding surveys every five or ten years in accordance with the desire of its citizens to get rid of tuberculosis.

As long as tuberculosis infection was universal among the young adults in a community, and apparently inescapable, segregation for treatment might have been considered largely as curative and could not be featured as a major preventive attack on the spread of the disease. Under such conditions the removal of aggravating secondary causes which reduce resistance to disease is a first-rate though indirect preventive measure applying to the entire population.

On the other hand, at a time like the present when infection has decreased to the point where only part of the young adult population is affected, then a direct attack through segregation of patients for treatment further reduces the level and increases the chance of escape from infection. This attack through segregation thus becomes a highly effective measure of prevention in that the uninfected are protected.

Removal of aggravating secondary causes then becomes operable only in the case of those who have been already infected and thus is only partially applicable as a preventive measure.

Finally, when only the minority are infected in young adult life, segregation becomes the major preventive measure as a means of protecting the majority who are uninfected; in this case, the removal of secondary aggravating causes becomes the minor preventive measure assisting in the protection of the infected minority.

At this juncture the opportune time has arrived to institute a program of eradication rather than of control.

In this latter phase of an antituberculosis campaign, emphasis should be focused and money spent not only on segregation but also on the elimination of infection. In other words, the slogan should be the eradication of tuberculosis by early discovery of spreaders, and also by segregation.

People should no longer be led to believe that they can obtain adequate protection merely by the removal of aggravating causes, such as poor living conditions, epidemics and other secondary predisposing causes; instead they should be encouraged to demand also the more adequate protection resulting from the elimination of infection.

In health work, as in agriculture, methods of eradication vary in accordance with the prevalence and noxiousness of weeds. The people of Canada know that tuberculosis is a bad weed, a perennial that sheds its seeds from year to year. When these weeds or cases are sparse, the best practice is to find them and remove them before the seeds are shed.

To accomplish this end everyone must learn to identify tuberculosis in the

seed, in the sprout, in the flower or in the ripe shelling. This is why preventive education should be pursued as never before in the schools, in the normal schools, in families and communities, and throughout Canada generally.

SUMMARY

1. Where, in accordance with an active program, the tuberculous sick are promptly admitted for hospital treatment, and where contacts and ex-patients are followed, the so-called well public includes only a small residuum of unknown spreaders. This was proved in the examination of 100,000 persons in Saskatchewan last year; the results showed unknown active cases to be one per 1,000.

2. Where active segregation for treatment has been practiced over a long period, the incidence of positive reactors to tuberculin decreases rapidly.

3. Segregation of patients for treatment is the method proved to be most effective in the elimination of infection. An adequate number of beds for treatment is still the greatest need in the campaign against tuberculosis in Canada.

4. The protection against tuberculosis of the unavoidably exposed, the nurses and other employees in general hospitals, mental hospitals and sanatoria, is the responsibility that rests upon all health workers and particularly on tuberculosis workers. Prophylactic vaccination with BCG of 1,800 persons in these groups in Saskatchewan since 1938 seems to have had a decided influence on the drop in incidence of tuberculosis in this group—only 10 persons have developed lesions to date.

5. With the advent of the photofluorographic film, the dream of economically discovering the unknown spreader has become a reality. No city or municipality is so small or large that it cannot raise the cost of case-finding through photofluorographic surveys. This method has demonstrated the practicability of the examination of cities, rural areas and entire provinces.

6. When only the minority are infected in young adult life, the opportune time has arrived to institute a program of eradication rather than control.

7. An intensive educational program in schools, homes and throughout the country supplemented by examination of the entire population every five to ten years would signalize the initiation of the eradication program.

SUMARIO

1. En los sitios en que de conformidad con un programa activo, se recibe sin tardanza a los tuberculosos enfermos en un hospital para tratamiento y se vigila a los contactos y antiguos enfermos, el llamado público sano sólo comprenderá un pequeño residuo de propagadores desconocidos. Esto quedó demostrado en el examen de 100,000 personas en Saskatchewan el año pasado: la proporción de casos activos desconocidos no pasó de 1 por 1,000.

2. En los sitios en que se ha practicado la segregación activa con mira al tratamiento durante un período prolongado, la frecuencia de reactores positivos a la tuberculina disminuye rápidamente.

3. La segregación de enfermos con mira al tratamiento es el método que ha resultado más eficaz para eliminar la infección. En la lucha antituberculosa en

el Canadá la necesidad mayor continúa siendo el contar con un número adecuado de camas para tratamiento.

4. La obligación que recae sobre todos los higienistas y en particular los que trabajan en tuberculosis consiste en proteger contra dicha enfermedad a los expuestos inevitablemente a ella, como enfermeras u otros empleados, en hospitales generales, manicomios y sanatorios. La vacunación profiláctica con BCG, desde 1938, de 1800 personas que pertencían a esos grupos en Saskatchewan, parece haber ejercido un influjo decidido sobre la baja de la tuberculosis en dicho sector: hasta la fecha sólo 10 personas han manifestado lesiones.

5. Con el advenimiento de la película foto-roentgenográfica se ha convertido en realidad el sueño de descubrir económicamente a los propagadores desconocidos. No hay ciudad ni municipalidad tan pequeña o grande que no pueda sufragar el costo del descubrimiento de casos por medio de encuestas foto-roentgenográficas. Con esa técnica ha quedado demostrada la factibilidad del examen de ciudades, distritos rurales y provincias enteras.

6. Cuando sólo se infecta la minoría de los adultos jóvenes, ha llegado la hora de instituir una obra de erradicación más bien que de mero control.

7. Un intenso programa educativo en escuelas, hogares, y en todo el país, complementado con el examen de toda la población cada 5 o 10 años, señalaría la iniciación del plan de erradicación.

COMPULSORY HOSPITALIZATION OF OPEN CASES OF TUBERCULOSIS[1]

ANDREW L. BANYAI AND ANTHONY V. CADDEN

It is paradoxical to see immense mass surveys for the early detection of tuberculosis, on the one hand, and the absence, inadequacy or laxity in execution of legal measures for the removal of open cases of tuberculosis from the community in large sections of the country, on the other hand. It is a matter of common knowledge that tuberculosis is bound to spread from a focus of open disease. Consequently, the problem of tuberculosis as a whole cannot be solved by sanatorium treatment and by an early discovery campaign alone unless effective laws are enacted and enforced without reticence for the compulsory hospitalization of tuberculosis carriers at large.

Tuberculosis carriers can be divided into three large groups: (*1*) Persons who, in spite of having active tuberculosis, do not realize that they are sick and are carrying on their occupation and usual activities, or who, while conscious of being sick, are not seeking medical attention, or, for some reason or another, are not informed about the true nature of their condition. (*2*) Patients with active disease who refuse to enter an institution. (*3*) Patients with active open tuberculosis who leave the sanatorium against medical advice. Persons belonging to the latter group, subsequent to their leaving the institution, are liable to carry on without proper medical and nursing care and are bound to exercise more and rest less than necessary for their treatment. Persons in these groups when they stay in their homes represent a health menace to their children, members of the household and their friends. Those who live in boarding houses constitute a health hazard in their particular environment. In addition, many of them frequent restaurants and stores and thus carry the infection to others. Some who are not debilitated and think that they are not physically incapacitated may and do find employment, particularly at the present time because of the war manpower shortage. Consequently, they become sources of infection to fellow employees or to the public when they are employed in hotels, restaurants, bakeries, stores and laundries, as we have seen it happen in so many instances; when they are employed as domestics, their disease may be transmitted to their employers or to children in the household; unfortunately, cases of pulmonary tuberculosis or tuberculous meningitis from such sources are not unfamiliar to the tuberculosis worker. All tuberculous patients at large who are able to be up and about are potentially dangerous to others when they are using public conveyances and mix with others at public gatherings.

The problem of patients who leave the sanatorium against medical advice is a constant and difficult one, particularly in institutions near large urban communities. A review of our past experience permits us to place these patients in the following groups: (*1*) Patients who feel that they are unable to get used to

[1] From the Muirdale Sanatorium, Wauwatosa, and from the Department of Medicine, Marquette University Medical School, Milwaukee, Wisconsin.

hospitalization either because of the necessity of adhering to a regulated regimen of living, or because of their inability or unwillingness to adapt themselves to staying with other patients. With reference to the latter, complaints and criticism may be endless, although fundamentally their cause may lie solely in the lack of coöperation and adjustment on the part of the patient. In this category belong patients who object to being moved from one room to another or from one ward to another and who cannot acquiesce in the refusal of unreasonable or frequent requests for leave of absence. (*2*) Patients who are superstitious or have religious prejudice. Their conviction or pretense may represent a strong impulse that results in the interruption of sanatorium treatment and in attempting to seek recovery from tuberculosis by auto-suggestion or quackery. (*3*) Patients who have marital or familial difficulties (proved or suspected infidelity, etc.), and feel that their presence in the home is the only means to solve the situation. (*4*) Patients who are worried over financial or economic difficulties, or who go into business although they realize that their disease is still active. (*5*) Patients who have a fear of or prejudice to surgical measures and having refused them they feel frustrated and their vanity is hurt. (*6*) Patients who disregard medical and institutional treatment entirely and instead seek the miracle of better climate. (*7*) Patients with *Wanderlust*. This group may well include those who, when hospitalized near large centres of population, cannot resist the lure of the Big City. (*8*) Common drifters and tramps who stay at the institution only long enough to be fattened up. (*9*) Patients who after a certain length of stay and improvement in their general condition become tired of the institutional environment and routine and who do not realize that feeling well does not necessarily mean being well. (*10*) Patients who are not receiving any form of active mechanical therapy and feel that they can carry out the same treatment outside of the institution. (*11*) Patients who are homesick. (*12*) Patients who go home to die.

A great deal of effort and time have been spent in counteracting the tendency of patients to leave tuberculosis institutions against medical advice. Recommendations and practices with any hope of promise have been made part of the daily procedure in sanatoria facing this problem. Special emphasis has been laid on adequate mental conditioning of the patient with particular reference to the discussion of his disease at the time of his admission and on subsequent occasions relative to his progress. The need for applying the personal touch in the relationship between patient and personnel is recognized; its attainment is greatly helped by establishing proper coöperation and coördination between physicians and nurses and all others attending to the patient's care and treatment. Selective placement and grouping of patients according to the stage of their disease, age, intellectual level, education, occupation, etc. are considered of value for making the patient contented. Similar purpose is served by early and well directed and supervised occupational and educational therapy. The assistance of social workers is called in to help the patient in solving his financial and other problems arising from his going to an institution, and for offering him all possible help for adjusting himself to his new environment. The segregation of the so-

called maximum benefit cases in a separate building or ward has been advocated as a useful and salutary measure, not only because these patients are in need of less medical and nursing care and may be allowed more activities than other patients but also because by such arrangement the therapeutic discipline of patients receiving active treatment can more efficiently be maintained and their cooperation, morale and will-to-get-well can be strengthened.

It is a matter of common knowledge that in spite of all concerted efforts there is a relatively high percentage of patients who are discharged without medical consent. Undoubtedly, this circumstance was responsible to no small degree for the institution of legislative measures pertaining to the compulsory hospitalization of patients with open tuberculosis. Relative to this issue the rules and regulations of the Wisconsin State Board of Health were codified in January, 1940, and revised in November, 1941. These statutes form the basis of the active campaign that is being conducted in Milwuakee County at the present time. A summary of their pertinent sections follows.

(*1*) Any individual afflicted with tuberculosis of the lungs in the communicable form, diagnosed as such by a licensed physician or as shown by X-ray or the presence of tubercle bacilli in the sputum in order to protect others from being infected may be quarantined on his premises by the local board of health or the health officer on the direction of the State Board of Health or State Health Officer, or by the full-time Medical Health Officer of any city or county with a population of 250,000 or more within his jurisdiction. (*2*) The same quarantine measure is applicable to patients afflicted with tuberculosis in a communicable form who leave the sanatorium against medical advice, if the health officer—as delegated by the law—considers quarantine necessary for the prevention of spread of tuberculosis. (*3*) The same authorities are empowered to release any individual from such quarantine when it is considered no longer necessary for protecting others from the disease or when such individual is being admitted to a tuberculosis sanatorium. (*4*) The individual who is afflicted with tuberculosis in a communicable form and who is incorrigible, careless, indifferent, and negligent concerning the exposure of others to the disease may be comitted by a court of record either to a tuberculosis sanatorium or to some other place where reasonable care can be given. (*5*) The provisions of the Children's Code classify as dangerous any home with children in it under the age of 18 years in which home there is a person who has tuberculosis in the communicable stage and who fails to obey the tuberculosis rules and regulations. Children living in such homes are considered neglected children and may be removed from the home.

Since these laws were passed by the Wisconsin Legislature it has been possible in a number of instances to hospitalize recalcitrant patients in the sanatorium by holding out to them the threat of quarantine or the prospect of court action. Still in other instances, it became necessary to go through regular legal procedures and obtain a court commitment. This has been accomplished with the cooperation of the local Health Department and the office of the District Attorney. Depending upon the individual aspects of the case, with particular reference to the potential public health menace represented by the patient, to home conditions and to his record of leaving the sanatorium against medical advice previously, these patients have been committed either to the County Sanatorium or

to the House of Correction of Milwaukee County. The latter is a penal institution receiving persons sentenced to not more than one year's imprisonment.

The care and treatment of patients committed by the Court to the Sanatorium differs in no way from that offered to patients who enter the institution voluntarily. One-half of the hospital unit of the House of Correction is reserved for tuberculous patients. Each patient is assigned to an individual cell, and there is no chance for contact with other inmates of the hospital unit. Each cell is equipped with a wash bowl and toilet facilities. The cells are well ventilated and have sufficient light for comfortable reading. The daily routine of these patients relative to rising, retiring and meals follows the regular schedule of the institution. The meals are served in the cells in separate dishes. The latter are washed by the patients so as to avoid possible contamination of others. Strict observance of precautionary measures are practiced concerning the disposal of sputum napkins, sputum bags, and the handling of their laundry. When weather permits the patients have the opportunity to sit or walk outdoors within the confines of the institution. The time allotted for this is arranged by the officer in charge and the physician in attendance. The patients have access to a circulating library in which books are provided according to their preferences. The library is under the supervision of the Sanatorium's Educational Therapy Department. Occupational therapy is being done along the same lines as practiced at the Sanatorium and has been planned by and is under the guidance of a graduate occupational therapist. Unquestionably, this type of creative activity contributes substantially to the patients' mental comfort and makes it easier for them to reconcile themselves to their situation. Every effort is being made to treat these individuals as patients and not as criminals, and impress upon them the fact that their stay there is not punishment but a matter of isolation. Each patient is provided with a radio and earphones.

Complete hospital records are carried with daily temperature and pulse charts, progress notes and periodic examination records. Because only men are being kept in this unit a graduate male nurse is in constant attendance. The patients are frequently seen by the physician in charge of the hospital unit and are visited once a week by a member of the sanatorium medical staff. Laboratory and X-ray work is arranged through the facilities of the Sanatorium which is only a twenty minute driving distance from the House of Correction. Emergency calls are covered by the Sanatorium staff. Until the present time only maximum benefit cases have been committed here, therefore pneumothorax treatment has not been an actual problem. If such necessity should arise, facilities are available at the ambulatory pneumothorax clinic of the County Dispensary which is within a short driving distance. At the discretion of the court and on the recommendaton of the physician in charge, patients may be transferred from the House of Correction to the Sanatorium if they become bedridden and need steady nursing care and close medical attention or for other justifiable reasons.

Legal measures more or less similar to that of Wisconsin, relative to the isolation of recalcitrant tuberculous patients, have been in effect in several states for various periods of time. In other states, laws governing the isolation of cases

with communicable diseases are resorted to for the removal of cases of open tuberculosis from the community.

The California Health and Safety Code, by vesting the power of isolating tuberculosis patients in the local health officer, makes the expediting of this matter simple and direct. Court procedures are started only when isolation is broken. Furthermore, it is significant that the health officer is authorized to examine persons *suspected* of having communicable tuberculosis. This statute makes it possible to detect potential sources of mass infection by persons who voluntarily might never request an examination or treatment.

Los Angeles County has a unique record relative to the isolation of patients with positive sputum. According to a survey published by Telford and Bogen (1) in 1942, more than 500 persons with active tuberculosis have been subjected to compulsory legal isolation in institutions since 1931 when the first legal proceedings were instituted. They were able to demonstrate a definite reduction in infection and disease rates in the contacts after the institutional isolation of the diseased person, in comparison with the corresponding figures during the period between the diagnosis and the isolation. On the basis of their statistical studies Telford and Bogen (1) concluded that the isolation of cases of open tuberculosis in Los Angeles County proved to be legally enforcible, financially feasible, socially acceptable and hygienically valuable.

The Connecticut laws pertaining to the imposition of quarantine on cases of communicable disease, although designed primarily for the emergency control of acute diseases, are potentially available for handling recalcitrant cases of tuberculosis. The quarantine powers are vested in local health officers. It is interesting to note that the quarantine order developed for this purpose specifically instructs the patient to proceed to a designated institution and to remain at such institution till he is duly authorized to leave. Furthermore, the order blank of the health officer includes a paragraph that orders the patient to obey all rules and regulations of the institution and to carry out faithfully all instructions of those responsible for his treatment.

Tuberculosis is included among the diseases for which the Sanitary Code of the District of Columbia authorizes isolation or quarantine of the person affected. According to Coulter (2), the penalty for infraction of this Sanitary Code is a $100 fine or thirty days in jail or both. In a recent communication he states that with nonpayment of the fine the patient is committed to the sanatorium for one hundred and eighty days plus thirty days: these patients are placed on probation and if they leave the institution against medical advice they are committed to a penal institution where provisions are available for their care. It is undoubtedly a very significant fact that for the past five years about 20 such cases have been brought up each year and in all cases the patient has been committed.

The control of recalcitrant tuberculous patients is accomplished by indirect means in Indiana. Auerbach (3) writes that, because there is no legislation concerning the compulsory hospitalization of tuberculous patients, the general quarantine law is resorted to or, in cases where there are children in the household, the juvenile court law is employed. He states that frequently the threat of quaran-

tine or that of the removal of children from the home was sufficient to bring about the acceptance of hospitalization by the tuberculous person. Similar procedures are used effectively in the State of Washington.

The recently revised Kansas statutes pertaining to this problem offer very explicit rules and regulations; they authorize the State Board of Health and the local health officer to place in complete isolation and quarantine the home of tuberculous persons who, from the public health standpoint, are considered a menace to the community. Furthermore, the local health officer is authorized to quarantine a person in the state tuberculosis sanatorium if such person refuses hospitalization or treatment if tuberculosis is diagnosed or reasonably suspected. From the standpoint of effectiveness, it is important that the proof of positive sputum as a prerequisite for enforced hospitalization is not demanded by the law. Furthermore, it is even of greater practical significance that the placement of persons known to have or suspected of having tuberculosis can be arranged by the health officer without a court order.

A similarly effective preventive program is laid down in the Michigan tuberculosis laws. The pertinent statutes are strengthened by a provision relative to the conduct of patients so isolated. Any patient so committed who neglects or refuses to obey the rules and regulations of the institution may be placed apart from other patients and restrained from leaving the institution. If a committed patient wilfully violates the rules and regulations of the institution or if he repeatedly conducts himself in a disorderly manner he may, after a due hearing, be committed to a penal institution maintained for persons convicted of disorderly conduct or vagrancy. When a tuberculous person is committed to a tuberculosis institution the length of his stay there is also defined by the law stating that, provided such person has obeyed the rules and regulations of such institution for a period of not less than sixty days, he may be discharged by the chief medical officer of the institution if and when the patient does not represent danger to the health and life of others any longer, or for any other reason deemed adequate and sufficient by the chief medical officer.

Chesley (4) states that compulsory isolation of tuberculous patients in institutions is being enforced in Minnesota. The procedure is based on statutes that authorize the local boards of health to isolate a person afflicted with tuberculosis in a public sanatorium or in some other suitable place of isolation, provided that the removal of the tuberculous person to a place of isolation is essential for the control and suppression of the disease in his particular locality and it is the only adequate way in which the community or the immediate family of the patient may be protected.

The communicable disease regulations of Missouri do not require placarding the home of a person who has open pulmonary tuberculosis, except if the precautions necessary for the prevention of the spread of the disease are not observed. The same section of the law contains a provision for the enforced hospitalization of patients who belong to this category.

Atchison (5) reports that under the laws of New Hampshire the Health Department has rather sweeping powers concerning quarantine of persons suspected

or proven to have a communicable disease. Inasmuch as the State Board of Health classifies tuberculosis as a reportable disease, quarantine has been instituted in cases of tuberculosis that refused adequate treatment. In many instances the patients finally coöperated rather than remain in quarantine. Recalcitrant patients are quarantined in one of the sanatoria or county institutions.

The New Jersey laws of 1942 contain definite and direct measures concerning a person who fails to obey the rules and regulations of the State Department of Health; it is stated that when a tuberculous person is an actual menace to the community or to children in his household he may be committed to the county hospital, or in case there is no county hospital in the county in which the patient resides, to a hospital in the same or in another county. The committment of a patient must be authorized by a judge of the court of common pleas. One section of this law is not unlike the Michigan statutes. It states that a person committed to the county tuberculosis hospital or any other hospital who fails to remain there or refuses or neglects to obey the rules and regulations of the institution may be isolated or separated from other persons and restrained from leaving the institution.

The definitions and directions laid down in the New York laws and regulations are formulated along similar lines as those in some of the other states; still they include certain points worthy of comment. (*1*) A health officer has the authority to send one of his public health nurses to cases of tuberculosis reported by practicing physicians to the Health Department. In every such case where the physician carries into effect the procedure and precautions by the Sanitary Code the public health nurse acts under the direction and supervision of the physician in charge of the case. (*2*) The law places specific emphasis on the existence of a probably large group of cases that come under the classification of tuberculosis carriers. (*3*) The health officer is obliged to carry out an investigation only in cases where a complaint is made to him by a physician. (*4*) According to the law the decision of the magistrate is optional in matters pertaining to the commitment of persons afflicted with or who are carriers of tuberculosis: the magistrate after due notice and hearing, if satisfied that the complaint of the health officer is well founded and that the person is a source of danger to others, may commit him to a county hospital for tuberculosis. Plunkett (6) commenting on this point states that it would be unwise to change the term "may commit" to "shall commit" and thereby making commitment virtually automatic in every case. By such a change the hope for justice in the lower courts would be futile. (*5*) The law permits the commitment of recalcitrant tuberculous persons to hospitals and institutions other than those maintained specifically for the care and treatment of tuberculous patients, provided facilities are available for their isolation. (*6*) Definitions for the discontinuance of the commitment are outlined as follows. The chief medical officer of the hospital or other institution to which a tuberculous person has been committed may discharge such person, if it can be done without danger to the health and life of others, provided the patient has obeyed the rules and regulations of the institution for a period of not less than sixty days. (*7*) There are two forms of disciplinary measures incorporated in

this law: *A*, any patient so committed who neglects or refuses to obey the rules or regulations of the institution may be placed apart from the other patients and restrained from leaving the institution; *B*, any tuberculous patient committed to an institution who wilfully violates the rules and regulations of the institution or repeatedly conducts himself in a disorderly manner may be committed by a court order of a magistrate to a penal institution to which persons convicted of disorderly conduct or vagrancy are committed, with the understanding that these tuberculous patients are kept separate from the other inmates.

Plunkett (6) reports that, in a survey conducted by the Tuberculosis Division of the New York State Department of Health, it was found that in upstate New York legal proceedings were initiated to commit tuberculosis cases under this law in 106 cases during the past five years. Commitments were obtained in 63, or 59 per cent, 58 were committed to sanatoria and 5 to jail. In contrast to these 63 admissions by legal measures there were about 17,500 adults with tuberculosis admitted to the state, county and city tuberculosis hospitals in the same section of the state during the same five-year period, that is, the law was invoked relatively infrequently, except in larger population areas.

The North Carolina General Assembly recently passed a bill without a dissenting vote which provides for the confinement of tuberculous patients with positive sputum who are wilfully negligent, in a division of the state sanatorium that is reserved for tuberculous prisoners. The confinement for the first offense is only for sixty days. McCain (7) reports that this legal procedure has already been resorted to in a number of patients who refused to stay in the sanatorium. He also mentions that in most instances it is only necessary to advise recalcitrant patients of the existence of the law to get them to take the proper precautions or to remain in the sanatorium until it is considered safe for them to leave.

The legislation relating to the control of cases of tuberculosis enacted by the General Assembly of Ohio in May, 1943 empowers the board of health to remove to a tuberculosis hospital any person suffering from tuberculosis when a recommendation to this effect is made by the health commissioner of the city or general health district where the patient resides, and when it is found that such person is a menace to public health and cannot receive suitable care and treatment at home. Here again the disposition in any individual case is delegated to the board of health with no need of court procedure. This law provides that such a person has the right to leave the state. In the latter instance, the health commissioner must notify the health authorities of the state to which removal was made.

DISCUSSION

It is not our intention to give in detail the tuberculosis statutes of all states where such statutes have been enacted, rather we aimed at presenting the salient aspects of some of them which together may serve as a composite model for further practical advancement in this field.

A review of the representative health laws in effect in various parts of the United States and the information received from the respective state health officers reveal that the difficulty in the management of incorrigible, uncoöpera-

tive and negligent tuberculous patients in the community—either before or after their admission to specialized institutions—is a universal and vexing experience throughout the country. More states have laws for quarantining the tuberculous patient than for enforced hospitalization. In states which have laws both for quarantining and for hospitalization, quarantining is more readily carried out than hospitalization. Paradoxically, in many instances quarantining the tuberculous patient may not be the most desirable procedure for the complete prevention of spread of the disease because, while the patient is taken out of the general circulation in the community, his contact with members of his own household is bound to be more frequent and the transmission of his disease to others about him more likely.

In some states in which no specific tuberculosis laws exist, general health laws are used for the isolation and institutionalization of cases of tuberculosis when necessary for the protection of the public. In others, although the statutes contain definite directions for the disposition of communicable disease cases, where no sufficient hospital or sanatorium beds are available for the isolation of recalcitrant tuberculous patients and where penal or corrective institutions have no adequate hospital wards for the care and treatment of these patients, the health authorities have been loathe to attempt enforced isolation.

The reasons recognized by the laws of various states for the compulsory hospitalization of the tuberculous are: (*1*) the refusal of a tuberculous patient to accept care and treatment of his disease; (*2*) tuberculosis in a communicable stage and (a) proper isolation cannot be maintained; (b) when the patient fails to observe the precautions necessary to prevent spreading of the disease in the household or in the community; (c) when the patient is *unable* to avoid exposure of his family to tuberculosis; (d) when the patient cannot receive suitable care and treatment at home.

The selection of the place of isolation is being solved on the basis of available physical facilities. Tuberculosis sanatoria or special units of such institutions, tuberculosis hospitals, any other hospital, penal or corrective institutions or any other place suitable for the care and treatment of these patients have been considered, specified and used.

The duration of commitment shows considerable variations. (*1*) Hospitalization may be discontinued any time at the discretion of the court. (*2*) The minimum length of stay is set at sixty days. (*3*) The maximum length of stay is set at seven months. (*4*) The patient remains isolated so long as he is, according to the opinion of the respective health officer, a menace to public health. Unless the term "menace to public health" is defined more explicitly, the release of the patient may be conditioned by negative sputum or gastric aspirations, by direct smear or by culture, or it may be determined by the patient's coöperative attitude, or on the basis of his home surroundings or other extraneous circumstances. (*5*) The patient is kept in isolation until released by the chief medical officer of the institution either because the patient's disease reached the noncommunicable stage, or for other *bona fide* reasons, such as removal to another state.

In some states the release of the committed tuberculous patient is qualified,

in addition to his not being a danger to the life and health of others, by the requirement that he must have obeyed the rules and regulations of the institution for a period of not less than sixty days.

The management of these patients after their commitment remains a serious problem. The character, temperament, emotional make-up, lack of understanding, antisocial tendencies and sharp resentment on the part of the patient so committed are the main factors responsible for the difficulties. The antagonistic and reckless conduct of these patients following their enforced hospitalization is well reflected by the investigations of Plunkett (7) who found that out of 63 committed patients in upstate New York 18, or 28 per cent, neglect or refuse to obey the rules of the institution or refuse to stay. Provisions are necessary for the disciplinary correction of these patients either by keeping the violators apart from other patients and restraining them from leaving the institution or by transferring them to a penal institution.

Gradations of the means for carrying out this part of a successful tuberculosis control may be chosen in the following order. (*1*) Advice to the patient by the private physician, health officer, public health nurse or social worker concerning the nature of the disease and the need for hospitalization. (*2*) Threat of quarantine and of enforced hospitalization. (*3*) Actual quarantining of the patient. (*4*) Threat of juvenile court proceedings. (*5*) Removal of children from the home by juvenile court order. (*6*) Commitment to a tuberculosis institution with the proviso that the patient may be placed on probation subsequently if his conduct justifies it. (*7*) Commitment to an institution until complete recovery. (*8*) Commitment to the corrective unit of a tuberculosis institution. (*9*) Temporary commitment to the hospital section of a penal institution followed by a transfer to a sanatorium. (*10*) Commitment to the hospital section of a penal institution until complete recovery from tuberculosis.

CONCLUSIONS

It is our conviction that, if we are to anticipate the complete eradication of tuberculosis in the reasonably near future, efforts directed toward the early discovery of this disease and the salutary results of the immense tuberculosis mass surveys must be supplemented by adequate universal legal measures for the enforced hospitalization of communicable cases of tuberculosis. The tuberculosis law should be explicit in its definitions, elastic and humane in its interpretation and judicious in its application.

These legislative measures must be supported by an intensive and continuous health educational campaign of the public as well as of members of the legislature and governing bodies, including federal, state, county and municipal units.

CONCLUSIONES

Abrigan los autores la convicción de que si va a lograrse la erradicación absoluta de la tuberculosis en un porvenir razonablemente próximo, los esfuerzos encaminados al descubrimiento temprano del mal y los saludables resultados de las inmensas encuestas colectivas relativas a la tuberculosis, deben ser com-

plementados con adecuadas providencias legales de aplicación universal, para la hospitalización obligatoria de los casos trasmisibles. Las leyes sobre tuberculosis deben mostrarse explícitas en sus definiciones, elásticas y humanas en su interpretación y juiciosas en su aplicación.

Esas medidas legislativas deben ser apoyadas por una intensa y continua campaña educativa en el público, así como entre los miembros de las legislaturas y ostros organismos supremos, incluso unidades federales, estatales y locales.

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THE TUBERCULOSIS REJECTEE[1]

EMIL BUNTA[2]

The problem of handling Selective Service registrants after their disqualification for military service because of tuberculosis is the responsibility of our public health officials. At the present time, there are many different systems operative throughout the country for following up tuberculosis rejectees. In Chicago, the follow-up of tuberculosis rejectees is undertaken by the City of Chicago Municipal Tuberculosis Sanitarium in participation with the Chicago Section, Tuberculosis Division, Medical Advisory Board No. 39, Illinois State Selective Service System.

RESULTS

The results of this study cover the period from September 30, 1941 to February 1, 1944. During that time, a total of 1,994 tuberculosis rejectees were reëxamined, 97 of whom had an examination on two separate occasions, making a grand total of 2,091 physical and X-ray examinations completed at the Medical Advisory Board. The list of 1,994 cases included 9 suspects with undetermined pulmonary lesions and 78 with nontuberculous pulmonary defects. The latter cases were excluded from further consideration and the analysis confined to the remaining 1,907 cases comprising the tuberculosis group.

Classified according to age, the tuberculosis group consisted of 65 registrants under twenty years of age; 941 others between the ages of twenty to twenty-nine; 825 in the thirty to thirty-nine, and 76 in the forty to forty-five age categories.

Listed racially, the tuberculosis series comprised 1,681 whites, 180 Negroes, 18 Mexicans, 15 Chinese, 10 Filipinos, 2 Indians and one Japanese.

A review of the Selective Service records disclosed that 1,351 of the 1,907, or 71 per cent of the tuberculosis cases were rejected at the Induction Center and 556, or 29 per cent, by the local draft boards.

Based on diagnoses made at the Medical Advisory Board, there was a total of 1,536, or 80.5 per cent of all tuberculosis rejectees, who showed X-ray evidence of minimal to far advanced reinfection types of pulmonary tuberculosis. Other forms of tuberculosis noted were: primary tuberculosis (247 cases), postprimary haematogenous or calcified miliary type pulmonary tuberculosis (38 cases), bone and joint tuberculosis (76 cases), genito-urinary tuberculosis (7 cases), tuberculosis of peritoneum (2 cases) and one case with cervical lymph node tuberculosis.

A comparative study of diagnoses made at the Induction Center and Medical Advisory Board, respectively, revealed only a few and negligible reversals of diagnosis. Five out of 1,120 cases rejected at the Induction Center as reinfection types of pulmonary tuberculosis were diagnosed as nonpulmonary tuberculosis at

[1] From the City of Chicago Municipal Tuberculosis Sanitarium, Dr. Frederick Tice, President of Board of Directors.

[2] Member of Chicago Section, Tuberculosis Division, Medical Advisory Board No. 39, Illinois State Selective Service System.

the Medical Advisory Board; and in 2 other cases, the diagnosis of a nonpulmonary tuberculosis established at the Induction Center was changed to reinfection pulmonary tuberculosis at the Medical Advisory Board. In 34 cases, the diagnosis of reinfection pulmonary tuberculosis originating at the Induction Center was changed to primary tuberculosis at the Medical Advisory Board; and 12 cases rejected at the Induction Center because of primary tuberculosis were subsequently diagnosed as reinfection pulmonary tuberculosis at the Medical Advisory Board.

X-ray follow-up at the Medical Advisory Board confirmed the diagnosis of therapeutic pneumothorax in 117 cases; phrenic paralysis in 42 cases and thoracoplasty in 17 cases rejected either at the Induction Center or by the local draft boards.

A total of 1,279, or 67.1 per cent of the 1,907 tuberculosis rejectees examined, were classified "4F" at the Medical Advisory Board and declared unfit for general military service. The remaining 628 registrants in this group were reclassified "1A" and recommended as eligible for induction. Making up the latter series were 463 men with minimal inactive and apparently arrested reinfection types of pulmonary tuberculosis, 21 borderline moderately advanced fibroid pulmonary cases and 142 selectees with demonstrable X-ray signs of a calcified primary complex. The vast majority of the reclassified individuals were asymptomatic, in good physical condition and, with but few exceptions, all were employed at their respective occupations. Inasmuch as several months elapsed since their original rejection because of presumably unstable lesions or lesions of questionable stability, and in view of the fact that Army physical standards were revised in the meantime, the Medical Advisory Board deemed it expedient to recommend that these registrants be remanded to the Induction Center for another examination.

Significant from the standpoint of case-finding was the disclosure that 1,431, or 75.4 per cent, of the 1,907 tuberculosis rejectees referred to the Medical Advisory Board were not registered with the Municipal Tuberculosis Sanitarium prior to their Selective Service examination. These cases were all checked through the Central Office of this organization which maintains a master file of all tuberculosis cases, including suspects, previously reported to the Chicago Board of Health. Included in the unregistered list were 170 under the care of private physicians. The entire group of new cases were registered with the Sanitarium organization and all, excepting those under treatment by private physicians, were placed under regular clinic supervision. Of the 1,431 new cases taken on, 1,129, or approximately 80 per cent, were reinfection types of pulmonary tuberculosis, 80 of which were far advanced cases. Thirteen of the latter had a positive sputum. The rest were sputum-negative cases or those in which the sputum status was unknown pending laboratory examination.

In line with the customary routine applying to all regular clinic cases, the individual X-ray films of the 1,431 newly registered Selective Service cases were transferred to the Collapse Therapy Clinic of our organization for review with the object of selecting suitable cases for ambulatory pneumothorax treatment. From this list, a total of 429 were selected for further study as prospective candidates

for collapse therapy. The remainder were excluded as treatment cases because they had either arrested lesions or active lesions which were too far advanced. Of the 429 selectees called in thus far, 191 have reported to the clinic and, of these, 59 are now undergoing pneumothorax treatment.

CONCLUSIONS

Routine chest roentgenography of Selective Service registrants in the process of preinduction examination was instrumental in weeding out large numbers of tuberculosis cases, the great majority of which proved to be new and unregistered. If the results attained in Chicago are any criterion, we may, in the long run, expect a substantial nation-wide incidence of tuberculosis in our adult male population. As a consequence, public health organizations in local communities throughout the country will be confronted with the task of tuberculosis rehabilitation in this respect, thus reducing the great cost to the Federal Government.

CONCLUSIONES

La radiografia torácica sistemática de los inscritos en el Servicio Selectivo, mientras se les examinaba antes del ingreso en las fuerzas militares, sirvió para excluir un gran número de casos de tuberculosis que en su inmensa mayoría resultaron ser nuevos y desconocidos. Si pueden tomarse como guía los resultados obtenidos en la cuidad de Chicago, es de esperar que a la larga habrá un coeficiente sustancial de tuberculosis entre los varones adultos de la nación en conjunto; a consecuencia de lo cual los organismos sanitarios de las distintas localidades del país se verán confrontadas con la tarea de rehabilitar a los tuberculosos, disminuyendo así el gran costo que esto acarrea al Gobierno Federal.

MEDIASTINAL HERNIATION IN ARTIFICIAL PNEUMOTHORAX[1]

Case Report of Bilateral Mediastinal Herniation in Bilateral Pneumothorax and Herniation of Extreme Size and Unusual Type

I. D. BOBROWITZ

Mediastinal herniation involves the mediastinal parietal pleura. Cunningham (1) has described the anatomy of the pleura as follows: "Different names are applied to the parietal pleura as it lines the different parts of the wall of the cavity in which the lung lies. Thus there are the costal pleura, the diaphragmatic pleura, the mediastinal pleura, and the cupula pleurae." "The mediastinal pleura extends from the dorsal surface of the ventral thoracic wall to the vertebral column," clothing the mediastinal structures between the two pleural cavities and "it is continuous with the costal pleura of its own side, both ventrally and dorsally, along two lines which are respectively termed the sternal and vertebral lines of pleural reflection, whilst inferiorly it becomes continuous with the diaphragmatic pleura of its own side at the base of the pericardium." The pulmonary visceral pleura becomes continuous with the mediastinal pleura at the root of the lung.

"The vertebral line of pleural reflection is that along which the costal pleura is continued ventrally from the vertebral column to become the mediastinal pleura. On the right side, above the root of the lung, the pleura passes from the bodies of the vertebrae on to the right side of the trachea, whilst lower down and dorsal to the pericardium, it passes from the vertebral bodies on to the esophagus. On the left side and above the arch of the aorta, the pleura, along this line of reflection, is carried from the vertebral column on to the esophagus and thoracic duct; below that level, it passes on to the thoracic aorta. In the superior part of the chest the right and left lines of reflection are placed well apart from each other and about equidistant from the median plane. As they are traced downwards they approach more closely to each other and deviate to the left, so that whilst the reflection on the right side takes place from the ventral aspect of the vertebral bodies, on the left side it takes place from the left aspect of the vertebral column. This is due to the position of the thoracic aorta.

"The sternal line of pleural reflection is that along which the costal pleura leaves the ventral thoracic wall to become the mediastinal pleura. The lines differ somewhat on the two sides, and in both cases show a tendency to deviate to the left. In the vicinity of the manubrium sterni the two pleural sacs are separated from each other by an angular interval. The lines of reflection at the superior thoracic aperture or inlet correspond to the sterno-clavicular joints. From those points, the lines, as they are traced downwards, converge behind the manubrium until at last they meet at its inferior border. There the two sacs come into contact with each other and the lines of reflection coincide. Thence

[1] From the Municipal Sanatorium, Otisville, New York (one of the hospitals of the Department of Hospitals, City of New York).

they proceed downwards on the back of the body of the sternum, with a slight deviation to the left of the median plane until a point immediately above the level of the sternal attachments of the 4th costal cartilages is reached, and there the two sacs part company. The line of reflection of the right pleura is continued downwards in a straight line to the xiphoid process where the sternal reflection line passes into the right diaphragmatic reflection line. Opposite the sternal attachment of the fourth costal cartilage, the reflection line of the left pleura deviates laterally and is continued downwards at a variable distance from the right pleura. Leaving the sternum the reflection line of the left pleura, passes downwards, parallel and close to the left margin of the sternum. . .to the sixth costal cartilage. There it turns laterally and downwards and passes into the diaphragmatic reflection line of the left side."

The mediastinum contains two weak areas, anterior and posterior. The mediastinal herniation, or the bulging or ballooning of the mediastinal parietal pleura across the midline occurs most commonly in the weakest point of the mediastinum, in the anterior mediastinum behind the sternum between the second and fourth sternocostal articulations where the right and left mediastinal parietal pleura are in apposition with each other. The areolar tissue, few lymph nodes, lymph vessels and minute vascular twigs in the anterior mediastinum form no barrier or resistance to mediastinal herniation. Less often, the herniation takes place in the lower posterior mediastinum "between the spine and aorta behind, and the heart and esophagus in the front" (2).

Mediastinal herniation occurs not infrequently during artificial pneumothorax therapy. Usually these herniations cause no untoward symptoms and are not considered particularly harmful or dangerous. The herniation is larger on expiration than inspiration, and often accompanies a mobile mediastinum. Ordinarily, a satisfactory pneumothorax can be maintained with little interference by a mediastinal hernia.

Although they are not often of extreme size, there have been reports of herniations of unusual degree, with complications. Acosta and Juan (3) describe giant herniation in a patient with bilateral pneumothorax with the hernia reaching the opposite thoracic wall, appearing like a pulmonary lobe, and during a pneumothorax refill this hernial pouch was punctured. Burrell (4) reports a case with a herniation of a pneumothorax reaching the opposite side in the fourth intercostal space, which, with cough, swelled between the ribs as a superficial tumor but which could be easily reduced.

Death has been attributed to mediastinal herniation. In his book, Heaton (5) notes a report of a patient's death from the pressure of the pneumothorax upon the heart and cardiac failure. A fatality as a result of the rupture of the pneumothorax hernia into the normal contralateral pleural cavity is described by Packard (6).

Shanks, Kerley and Twining (7) note that mediastinal herniation is of little significance in a mobile mediastinum as it results without excessive pressure, but with a rigid mediastinum it does not occur without excessive pressure and the sudden production of the hernia may cause shock and death.

This report is of a case with several unusual features, with bilateral mediastinal herniation in bilateral pneumothorax and mediastinal herniation of extreme size and unusual type.

CASE REPORT

The patient, *P. M.*, a twenty-four year old single white male, restaurant worker, was admitted to the Municipal Sanatorium September 18, 1941. His illness began in December, 1939, when a rectal abscess developed. This was incised and drained in May, 1940. An X-ray film of the chest at that time revealed a productive lesion in the left first anterior intercostal space with a suspicious area of clearing at its axillary portion. In June, 1941 he required another operation for a perianal abscess and fistulous tracts. The histological examination of the perirectal tissue revealed tuberculosis.

On admission to the Sanatorium he had no complaints and chest examination revealed no abnormal physical findings. The X-ray films showed an oval shaped moderately thick walled cavity, 1 x 2 cm., at the level of the left first rib. Small coalescent mottled infiltrations were present in the right first anterior interspace. The patient was placed on complete bed-rest. During September and October one sputum and gastric culture were reported positive although several other sputa were negative. Another X-ray examination at the end of October showed no changes.

Because of the cavity and positive sputum and gastric cultures, left artificial pneumothorax was started October 30, 1941. Good negative readings were obtained and 300 cc. of air was given at the initial pneumothorax treatment. After three consecutive daily refills treatments were continued every three days during the first month and then twice a week. An average of 350 to 400 cc. of air was given at each refill with average readings of -9 -5, -7 -4. Within two weeks after initiation of pneumothorax a 40 per cent collapse of the left upper and left lower lobes was present. No adhesions could be seen. The left upper lobe cavity was clearly visible, 1 x 1.5 cm., surrounded by dense perifocal infiltrations. The trachea, heart and mediastinum were shifted only one-half inch to the right.

During the next month the pneumothorax collapse changed little and the cavity became only slightly smaller. Sputa and gastrics were occasionally positive and cultures were usually positive. Refills were continued twice weekly until March, 1942 with average injections of 320 cc. of air and readings that, as heretofore, were always negative, -10 -4, -8 -3. The pneumothorax had gradually increased with the left upper lobe 80 per cent and the lower lobe about 70 per cent collapsed. The left upper lobe was uniformly dense, with its apex at the level of the seventh posterior rib and the cavity was no longer visible. The infiltration in the right upper lobe was unchanged. Sputa were consistently negative with an occasional positive gastric culture. Slight cough and expectoration, previously not present, appeared.

At this time, March, 1942, a herniation of the mediastinum became evident as a thin semicircular line on the right side, between the levels of the fifth and ninth ribs posteriorly, with the convexity toward the uncollapsed right lung. The herniation gradually increased in size so that in a few weeks it almost reached the opposite axilla on expiration, and on inspiration it merged with the mediastinum. The slight shift of the heart to the right had not changed.

To decrease the herniation and maintain the left pneumothorax, smaller refills of 170 cc. of air were given three times a week with readings of -10 -3, -8 -2. Larger amounts of air only exaggerated the degree of herniation without much increase in the lung collapse. With this pneumothorax, sputa continued negative but the gastric concentrates and cultures were positive.

Even though no adhesions were visible on X-ray examination, a thoracoscopy was recommended with the idea that perhaps posterior or mediastinal adhesions might be present. On May 23, 1942 a left thoracoscopy was performed, but no adhesions were seen with the patient placed in different positions. The sputum was negative from June to September, and small refills were continued every three days.

There were no significant changes until October, 1942. Films on expiration then revealed a very marked mediastinal herniation to the right. The hernia was outlined by a line extending below the level of the right diaphragm in the tenth posterior interspace one-half inch from the right cardiac border, and curving upward and laterally in an arc-like fashion, with the convexity to the right, reaching the axillary chest wall at the level of the fourth posterior or third anterior rib. The upper limit of the hernial line could not be seen. No lung markings were visible in the right upper chest from the apex to the level of the fifth posterior rib, and the appearance was typical of a pneumothorax space. With expiration the heart showed a one-inch deviation to the right.

On inspiration, the herniation appeared as a slight bulge to the right of the mediastinum and it was marked by a linear density extending upward in a vertical direction from the level of the ninth posterior or fourth anterior rib one-half inch from the cardiac border to the level of the sixth posterior or second anterior rib, and then in a horizontal manner along the first anterior interspace, but the line was not definitely seen beyond the middle half of the interspace. Only the apex showed a lack of lung markings. Oblique and lateral films showed the herniation to be in the anterior mediastinum.

Films on inspiration and expiration in lordotic position also revealed the pneumothorax space in the right upper chest with the lung markings at the level of the second posterior rib on inspiration, and the fourth posterior rib on expiration. These lordotic views showed that the apical lung margin had not the typical appearance of a rounded upper lobe. On inspiration the lung margin was horizontal, with a downward dip at the mediastinum, and on expiration (figure 1) the lung line had a concave shape with the base of the concavity in the direction of the diaphragm; the ends were adherent at the axilla and mediastinum. Figure 1, a lordotic apical view taken on expiration, shows the regular pneumothorax of the left side and the new pneumothorax space in the upper right chest with the apical concave lung margin and the mediastinal herniation line.

It was believed that the pneumothorax in the right apex resulted from the left mediastinal hernia, or was due to a partial right spontaneous pneumothorax. The patient complained only of cough and scant expectoration. However, a spontaneous pneumothorax could occur without typical symptoms or with no symptoms at all. Physical examination was not conclusive, as the breath sounds were diminished in the right apex.

To determine the extent of the herniation and explain the air in the right apex, it was decided to instill normal saline solution into the left pleural space and to see if it would, by posturing the patient, appear in the right apex. This was done December 24, 1942. There had been no X-ray changes since October. Fluoroscopic examination was confirmatory of the X-ray findings; no lung markings were seen in the right apex and the space that seemed to be a pneumothorax space was larger on expiration than inspiration. Three hundred cc. of physiological saline solution was injected into the left pleural space while the patient was kept in a right lateral Trendelenburg position. Immediately after injection, fluid appeared in the right apex and collected in its lateral aspect. A film taken in the right lateral Trendelenburg position (figure 2) showed a fluid level in the right apex with fluid collected along the lateral chest wall from the apex to the fourth posterior rib. It also showed fluid in the left chest, collected in the medial aspect from the apex to the sixth interspace posteriorly. Examination in the upright position (figure 3) revealed

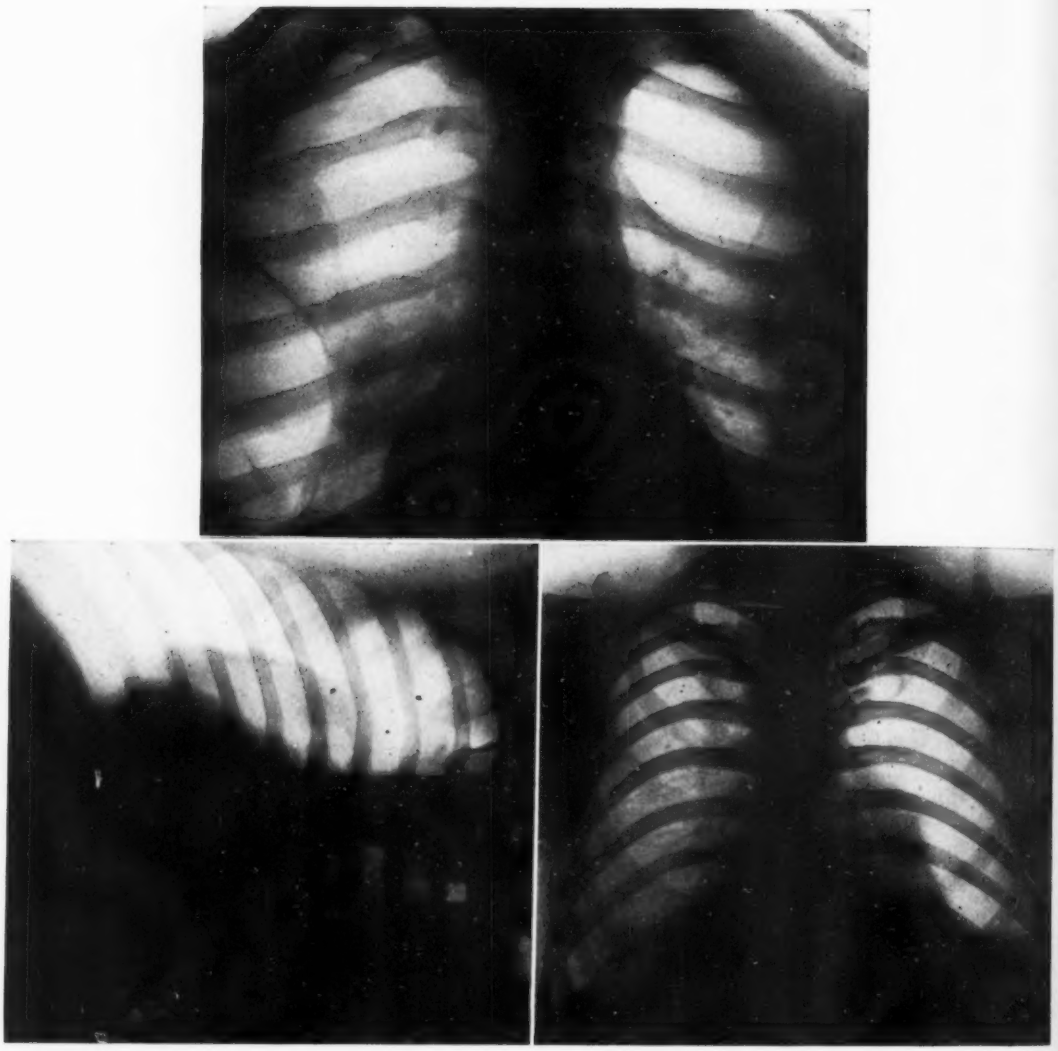

FIG. 1. (Top.) October 16, 1942. Apical view on expiration in lordotic position. Pneumothorax, left, with good collapse of the left lung. Heart shifted to right. Pneumothorax in right apical field. Lung markings at the level of the fourth posterior rib and apical lung margin assume a concave shape. The base of the concavity is in the direction of the diaphragm and the ends are adherent at the axilla and mediastinum. Mediastinal herniation appears as a line extending from lower cardiac region at level of seventh posterior interspace, curving upwards and laterally, reaching the axillary chest wall at the level of the third posterior interspace.

FIG. 2. (Lower left.) December 24, 1942. Patient in right lateral Trendelenburg position immediately after instillation of 300 cc. of normal saline into left pleural space. Pneumothorax left with well collapsed left lung. Fluid is collected in left upper chest along medial aspect. Hydropneumothorax space in right upper chest with fluid along lateral chest wall. Rest of right lung shows normal lung markings.

FIG. 3. (Lower right.) December 24, 1942. Patient in upright position after instillation of 300 cc. of saline into left pleural space. Hydropneumothorax left with fluid at the level of the tenth posterior interspace. Left lung is about 80 per cent collapsed. Heart is shifted slightly to right. Hydropneumothorax on right with fluid at the level of the tenth posterior interspace and limited by the heart medially and by the line of mediastinal herniation laterally. This mediastinal herniation appears as linear density originating below diaphragm and extending upwards and laterally, reaching the anterior axillary line at the level of the third anterior rib. No lung markings are visible in the right upper chest from the apex to the fifth posterior rib.

two fluid levels, one in the left pleural space at the level of the tenth posterior interspace and above the highest point of the diaphragm, and another in the right chest at a slightly higher level than on the left, that is at the level of the tenth posterior interspace, bounded by the heart medially and laterally, by the linear density described above as the limit of the mediastinal hernia.

This saline instillation proved that the pneumothorax space in the right hemithorax was not a result of a right spontaneous pneumothorax but communicated with the left pleural space and that the air pocket was limited on the right by the mediastinal herniation of the left pneumothorax. This mediastinal herniation of the left pneumothorax space delineated an air pocket that completely occupied the right apex and a part of the hemithorax below, to a level below the right diaphragm; the herniation was much greater on expiration than inspiration. The fluoroscopic and X-ray examinations made after the saline instillation were conducted with Dr. J. E. Noll, Visiting Roentgenologist.

Slight pain in the left chest appeared two and one-half hours after the saline instillation, and the temperature rose to 99.6°F.; the respiratory rate was 22 and pulse rate 92. Two and one-half hours later the pain had increased and the temperature was 102°F., the pulse rate 122 and respirations 40. The patient was made comfortable with sedatives, and by the next day the pain was much less and there was no dyspnoea. All complaints disappeared by the third day and the temperature became normal on the fourth day, and fever did not recur. There was no reactional increase in the fluid and only a small amount remained covering the left costophrenic sinus.

Up to now the left pneumothorax had been maintained by small frequent refills, with an 80 per cent and 70 per cent collapse of the left upper and lower lobes, respectively. The sputum had again become positive in November and December, 1942 and, as the massive herniation would not permit a more effective collapse on the left, and because the extreme degree of herniation could itself be harmful, it was decided to allow the left lung to reëxpand. Therefore, from December 19, 1942 and for a period of two months until February 19, 1943, no air refills were given on the left side. Gradual reëxpansion of the left lung occurred and the mediastinal herniation became smaller and smaller. By February 2, 1943 expiration showed a marked decrease in the mediastinal herniation. It now appeared as a small circular bulge in the right chest at the level of the sixth to tenth posterior ribs, or second to fourth anterior ribs, and one-half inch from the heart shadow in its upper third, and one inch in the lower two-thirds. No herniation was visible on inspiration. The left upper lobe was only 50 per cent collapsed and no cavity was visible within it. The left lower lobe was marginally collapsed and fluid covered the left costophrenic sinus. No pneumothorax was seen in the right apical field. Films on inspiration and expiration in lordotic position no longer showed the previously described air space in the right upper chest.

Within the infiltration in the right first interspace a small area of translucency was seen suggesting a cavity. The sputum had remained positive and, inasmuch as the mediastinal hernia was controlled and the cavity in the right apex was undoubtedly responsible for the positive sputum, it was decided to maintain the pneumothorax on the left and institute pneumothorax on the right side.

A right pneumothorax was initiated February 10, 1943 with 200 cc. of air and negative readings, and the next two successive days refills of 400 cc. of air were given, with readings of -7 -4, -6 -3. Within three days, X-ray and fluoroscopic examination revealed the left lung unchanged compared to February 2, 1943. A partial pneumothorax was present on the right, and the right apex had a rounded shape and was at the level of the fifth posterior rib, with a cavity visible in the right upper lobe infiltration, and a marginal

collapse of the rest of the lung. On inspiration the mediastinum was slightly shifted to the left, and a mediastinal herniation appeared on the left as a kidney-shaped shadow extending from the first to the fourth anterior ribs, with the convexity to the left and at its greatest width in the centre, two and one-fourth inches from the heart. On expiration the pneumothorax space appeared to increase on both sides but no mediastinal hernia was present though the mediastinum moved slightly to the right. This was the first time the mediastinal herniation was more apparent on inspiration than expiration, and the first occurrence of herniation in the left pleural space. A lateral view showed this mediastinal hernia of the right pneumothorax space also to be in the anterior mediastinum between the first and fourth ribs anteriorly, though the pole of the kidney-shaped shadow, or the area through which the herniation occurred, was at the level of the second and third ribs anteriorly.

For the first six weeks after the right pneumothorax, refills were scheduled on the right every three days and on the left every six days. Whenever a refill was given on the left a simultaneous refill was given on the right. In this manner better control was exercised over the herniation and mediastinal mobility. Refills on the left averaged 310 cc. with readings of −11 −5, −8 −4, and on the right, 285 cc. with readings of −7 −4, −6 −2. It should be noted that the pressures were always negative.

On March 23, 1943 film on inspiration showed a slight shift of the mediastinum to the left. The collapse of the left lung was unchanged, no fluid was present and no definite cavity was seen in the left upper lobe. The pneumothorax on the right was slightly increased, with about a 25 per cent collapse of the right upper lobe, with the apex at the level of the fourth posterior rib, and the rest of the right lung marginally collapsed. Areas of translucency were still visible in the right upper lobe infiltration. With inspiration, there was a slight mediastinal herniation to the left from the level of the first to the fourth anterior ribs, with the linear curved density forming a convexity to the left and with the maximum width at the centre three-fourths inches from the cardiac border.

Whereas on inspiration no part of the heart was to the right of the spine, on expiration the heart deviated moderately to the right, two inches beyond the right lateral margin of the spine. With expiration the left pneumothorax space seemed to increase, with 75 per cent collapse of the left upper lobe, 55 per cent of the left lower lobe. The right upper lobe collapse increased to about 35 per cent, with the right apex at the fifth posterior interspace. The translucent area was still visible in the right upper. On expiration, there was a mediastinal herniation to the right, of slight degree, marked by a curved line extending from the first to fourth anterior ribs and one inch from the lateral margin of the spine. Thus a most interesting condition existed: a mediastinal herniation present in the left chest on inspiration, and in the right chest on expiration—a bilateral mediastinal herniation in bilateral pneumothorax.

Left pneumothorax was continued at weekly intervals, with average refills of 310 cc. and readings of −11 −4, −8 −2, and on the right, refills were given every three days with 250 cc. and readings of −7 −3, −6 −1. Sputa continued alternately positive and negative, though the last two, prior to the patient's discharge on July 1, 1943, were negative.

The final X-ray film of June 17, 1943 showed the collapse of both lungs slightly increased and no cavities visible in either upper lobe. On inspiration no mediastinal herniation was present and the heart and trachea were in the midline. On expiration the heart shifted slightly to the right and a mediastinal herniation appeared on the right side with convexity to the right, extending from the first to fourth anterior ribs, with the maximum width in the centre one and three-fourths inches from the lateral edge of the spine.

The patient was transferred to a City hospital July 1, 1943 for continuation of treatment.

Other laboratory findings were negative. Although he had no dyspnoea, vital capacity determinations were reported to have decreased from 100 per cent of normal in September, 1941 to 44 per cent on June 10, 1943.

COMMENT

This case illustrates an unusual example of mediastinal herniation with artificial pneumothorax. The pliability and stretching of the mediastinal pleura were remarkable. In this instance, in a patient with left artificial pneumothorax, a mediastinal herniation extended across the midline to reach below the right diaphragm and to the right chest wall and into the right apex, displacing or peeling away the contralateral lung and filling out the entire apex and forming a huge pneumothorax space.

Another very interesting feature of the case occurred with the institution of right artificial pneumothorax, for, in the presence of bilateral pneumothorax, bilateral mediastinal herniation became evident, and the great mobility of the mediastinal pleura was illustrated by the deviation of both pleural septa into the opposite pleural spaces—bilateral mediastinal herniation in bilateral pneumothorax. Both herniations traversed the anterior mediastinum.

A diagnostic problem arose as to whether the apparent pneumothorax in the right upper chest was the result of the left herniation or of a right spontaneous pneumothorax. The differential diagnosis was made by instillation of saline in the left pneumothorax space. On posturing the patient, this revealed a fluid collection in the right apex, indicating a left pneumothorax herniation into the right hemithorax. A temporary moderate reaction followed the saline instillation.

Additional proof that the pneumothorax in the right apex was due to the left mediastinal hernia was furnished by the institution of right artificial pneumothorax. The right lung, collapsed by artificial pneumothorax, showed a rounded apex, whereas the pneumothorax in the right apex, due to the herniation, revealed (figure 1) an unusual, atypical, apical lung margin.

The extreme degree of herniation of the left mediastinal parietal pleura, the occurrence of the bilateral mediastinal herniation and the rapid appearance of the herniation of the right mediastinal parietal pleura would indicate that a developmental or congenital factor was present which determined the elasticity and character of the mediastinal pleura.

The area through which the mediastinal herniation occurs, the retrosternal weak point in the anterior mediastinum, is constant, though the extent of the herniation in the pleural space can vary greatly in size.

Inartificial pneumothorax there is no relation between the ease of deviation of the heart and the degree of mobility of the mediastinal pleura. This patient showed a slight shifting of the heart and a marked mediastinal herniation. The heart and mediastinal hernia move in the same direction during inspiration and expiration.

In ordinary unilateral artificial pneumothorax the mediastinal herniation is

greater on expiration than inspiration. On expiration, with a smaller chest cage, the herniation with its pneumothorax air has less room and encroaches on the uncollapsed hemithorax. The motion of the mediastinal herniation results from the difference in the pleural pressures and the variation in the degree of lung expansion and volume of air exchange in the lungs. The hernia on inspiration moves away from the lung with the greatest expansion and air intake, and with expiration moves toward the lung with greatest exhalation and loss of air. In bilateral pneumothorax, the herniation is not necessarily larger on expiration and in our case, on one occasion, the herniation was more evident on inspiration than expiration. In bilateral pneumothorax the mediastinal parietal pleura on both sides may herniate or differ in its laxity and the degree of collapse and expansion of the lungs will vary, as will the pleural pressures.

Mediastinal herniation can form and become more severe, even though all pneumothorax refills are at a subatmospheric or negative pressure; small amounts of air can cause great variations in the degree of herniation. The mediastinal herniation appeared on both sides in the presence of negative intrapleural pressures.

Mediastinal herniation can be extreme without any symptoms; our patient had a tremendous herniation with no dyspnoea, chest pain nor other symptoms.

Mediastinal herniation is exaggerated on expiration, and the size of the herniation should not be judged by routine inspiration films. Even with slight pressure changes during pneumothorax therapy, there may be marked difference in the extent of the herniation. In our case, the herniation was slight on inspiration and very marked on expiration.

Mediastinal herniation may reveal itself at various times and it may become evident very soon after the pneumothorax is started. The left pneumothorax showed a herniation during four months, but the right pneumothorax herniation was apparent only after three days.

The temporary cessation of pneumothorax refills can cause a very marked herniation to disappear and then it can be controlled by small infrequent refills.

If during pneumothorax refills the pressures show little or no change with administration of air, it should be remembered that a mediastinal herniation may be responsible rather than a deviation of the heart and mediastinum.

Pneumothorax cases should be checked fluoroscopically very frequently, preferably at each refill.

CONCLUSION

An unusual case has been presented of bilateral mediastinal herniation in bilateral pneumothorax, with the herniation on one side reaching an extreme size.

CONCLUSIONES

Preséntase un caso extraño de hernia bilateral del mediastino en un neumotórax bilateral, en el que la hernia en un lado alcanzó un tamaño inusitado.

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EFFECT OF PROMIN ON EXPERIMENTAL TUBERCULOSIS

A. R. ARMSTRONG,[1] M. V. RAE,[1] C. C. LUCAS[2] AND P. H. GREEY[2]

Promin[3] has been shown to alter the course of experimental tuberculosis, but only under certain well defined conditions. Preliminary studies by the authors in 1940 failed to disclose any therapeutic activity whatsoever. However, following publication by Feldman, Hinshaw and Moses (1, 2) of reports in which this substance was stated to modify the disease in guinea pigs, the compound was reinvestigated more fully. The details of the experiments and the results are presented in tables 1 and 2.

TABLE 1

Treatment of experimental tuberculosis in guinea pigs with promin—Details of infection and dosage of promin

EXPERIMENT NUMBER	DOSE OF TUBERCLE BACILLI	STRAIN OF TUBERCLE BACILLI	DETAILS OF TREATMENT	BLOOD CONCENTRATION OF DRUG
1	0.05 cc. of suspension showing Gaffky II on smear, intraperitoneally	Mountain Sanatorium strain	400 mg. on food for 21 days	Not estimated
2	0.05 cc. of suspension showing Gaffky II on smear, intraperitoneally	Mountain Sanatorium strain	400 mg. on food for 40 days	3.7 to 10 mg. per cent
3	0.05 cc. of suspension showing Gaffky II on smear, intraperitoneally	Mountain Sanatorium strain	500 mg. on food and by stomach tube for 42 days	Not estimated
4	0.005 mg., intraperitoneally	Mountain Sanatorium strain	300 mg. on food for 9 months	2.5 to 8 mg. per cent
5	0.005 mg., intraperitoneally	H37 strain	300 mg. on food for 10 months	Not estimated

The procedure in the first three experiments was that devised in our laboratory (see table 1, experiments 1, 2, and 3). The modification used in the last two experiments was, as nearly as possible, identical with the Mayo technique except for the strain of organism in experiment 4.

Whereas no demonstrable activity of promin can be observed on inspection of the results of experients 1 to 3 inclusive (table 2), a very definite effect is to be seen in the outcome of experiments 4 and 5. The survival times of the treated

[1] Mountain Sanatorium, Hamilton, Ontario.

[2] University of Toronto, Toronto, Ontario.

[3] Sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′-dextrose sulfonate. The promin used in these experiments was kindly provided by Parke, Davis & Company, Detroit, Michigan, U. S. A.

TABLE 2

Treatment of experimental tuberculosis in guinea pigs with promin—Results of treatment

EXPERIMENT NUMBER	SERIES	NUMBER OF GUINEA PIGS	WEIGHT AT START	WEIGHT AT DEATH	ALL SKIN TESTS POSITIVE	MAXIMUM LENGTH OF SURVIVAL	AVERAGE LENGTH OF SURVIVAL	PATHOLOGICAL CHANGES
			grams	*grams*	*weeks*	*weeks*	*weeks*	
1	Test	25	—	—	3	30	22½	Extensive disease in all organs
	Control	25	—	—	3	35	19	Extensive disease in all organs
2	Test	25	—	—	6	40	16	Many died of nontuberculous disease. Other had tuberculosis similar to that in controls
	Control	25	—	—	6	24	12	Extensive disease in all organs
3	Test	25	—	—	6	36	14	Extensive disease in all organs
	Control	25	—	—	6	22	13	Extensive disease in all organs
4	Test	25	400–600	500–1000 Av. 735	12	44 (killed)	40+	Spleen: 6: 0; 6: +; 10: ++; 1: +++; 2: ++++ — Liver: 6: 0; 3: +; 9: ++; 6: +++; 1: ++++ — Lungs: 3: 0; 9: +; 10: ++; 3: +++
	Control	25	400–600	380–650 Av. 515	8 (1 exception died of tuberculosis)	36	20	Extensive disease in all organs
5	Test	24	400–600	450–1000 Av. 805	12 (1 exception died of tuberculosis)	40 (killed)	38+	Spleen: 16: 0; 3: +; 3: ++; 1: +++; 1: ++++ — Liver: 19: 0; 3: +; 1: ++; 1: +++ — Lungs: 17: 0; 4: +; 3: ++
	Control	23	400–600	360–850 Av. 495	9	32	21	Very extensive disease in all organs

animals in the latter experiments are, on the average, about twice as long as those for the untreated controls. Further evidence of the effect of promin is to be found in the fact that all the treated animals gained in weight, whereas the control guinea pigs did not. In one set, the difference between the average of the weights of the test animals and that of the controls was 220 g., in the other 310 g.

The clear-cut demonstration of the effectiveness of promin against the tuberculous process in the last two experiments indicates that the negative results in the first three were due to unsuitable conditions of testing—probably either insufficient prolongation of the promin feeding or too heavy an infecting dose of tubercle bacilli. Further experimentation would be required to clarify this point, but the study has had, temporarily, to be abandoned.

The findings illustrate the fact that detection of chemotherapeutic activity in a new compound may offer unexpected difficulties; they emphasize the importance of consideration of each of the several variables in such an experiment—mass of infecting organisims, dose of drug, frequency of administration and duration of treatment.

SUMMARY

Promin (sodium salt of p,p′-diamino-diphenyl-sulfone-N,N′-dextrose sulfonate), under strictly defined experimental conditions, influences favorably the course of experimental tuberculosis in guinea pigs.

SUMARIO

La promina (sal sódica del p,p′-diamino-difenil-sulfona-N,N′-dextrosa sulfonato) en ciertas condiciones bien definidas de experimentación afecta favorablemente la evolución de la tuberculosis pulmonar en el cobayo.

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SULFANILAMIDE AND SULFAPYRIDINE IN EXPERIMENTAL TUBERCULOSIS[1,2]

C. RICHARD SMITH

Rich and Follis (1) first reported the effect of sulfanilamide, Feldman and Hinshaw (2) that of sulfapyridine on experimental tuberculosis. Meanwhile numerous publications have appeared on the use of various sulfonamides and sulfones, for reviews of which the reader is referred to Smith, Emmart and Westfall (3) and Callomon (4).

IN VITRO EXPERIMENT

In our experiment the drugs were incorporated in Petragnani's culture medium in varying strengths, sodium hydroxide being used to promote solution. One set of tubes was planted with a suspension of tubercle bacilli (strain 88 isolated in this laboratory) containing 0.1 mg. moist culture per cc., another set with a suspension containing 0.001 mg. per cc., 2 drops to a tube.

For sulfanilamide, no inhibition was noted at drug concentrations of 1:5,000 or less. There was marked inhibition at 1:1,000 when the inoculum contained 0.1 mg. tubercle bacilli per cc. and complete inhibition when it contained 0.001 mg. With sulfapyridine there was no inhibition at drug concentrations of 1:10,000 or less; moderate inhibition of the growth of both inocula at 1:5,000; and complete prevention of growth for both inoculation strengths at 1:1,000.

ANIMAL EXPERIMENT

Ninety-six guinea pigs were separated into four groups, as follows:

A. 24 animals, not infected but treated with
   1. Sulfanilamide (12 animals) and
   2. Sulfapyridine (12 animals).

B. 24 animals, infected with tubercle bacilli but not treated.

C. 24 animals, infected and treated with sulfanilamide.

D. 24 animals, infected and treated with sulfapyridine.

Each group was composed of an equal number of tuberculin-negative males and females kept separately, 6 to a cage. The average weights of the guinea pigs in each group were 342, 336, 335 and 334 g., respectively.

Infection was by subcutaneous inoculation in the right flank with 1 cc. of a suspension containing 0.000,1 mg. moist culture of virulent human tubercle bacilli (strain 88) seven weeks old.

Drug treatment was started on the same day on which the infection was given. The daily dosage in either case was 340 mg., given in 5 portions at 8:00 a.m.,

[1] From the Barlow Sanatorium, Los Angeles, California.

[2] This experiment was carried out in 1939, the study not being completed then because of illness. Although now, in a sense, obsolete, it is felt that a brief accounting should be made.

10:00 a.m., 12:00 m., 2:00 p.m. and 4:00 p.m. The powder was introduced into the pharynx whence it was invariably swallowed.

The experiment was planned to run thirty days.

Blood chemistry in group A animals: Blood levels of the free drug ranged from 10 to 32 mg. per cent during the day, but fell off during the night to between 1 and 5 mg. per cent in the early morning. The sulfanilamide levels rose rapidly following treatment to maxima at 10:30 a.m. and 4:30 p.m. The average level of the two drugs at 4:30 p.m. was the same, 26 mg. per cent. Following this the sulfanilamide concentration dropped more rapidly to an average of 6.9 mg. at 8:00 p.m., 4.3 mg. at 10:45 p.m. and 1.8 mg. per cent at 7:40 a.m., as compared with average sulfapyridine concentrations of 18.4, 10.5 and 3.5 mg. per cent, respectively.

Tuberculin tests: Intracutaneous injection of 2.5 mg. OT on the fifteenth day elicited no allergy in response in group A, 16 positive reactions in group B, 2 positives in group C and 2 in group D.

Postmortem findings: One group C animal died on the twenty-fourth day, one on the twenty-ninth. The remaining animals were sacrificed on the thirtieth to thirty-third days. In all cases death and autopsy were in sets, including one from each group of the same sex and comparable weight.

The data for gross and microscopical estimates of disease were placed in arrays of increasing values. After separating the first group of negative or zero values, the balance of each array was divided into four roughly equal parts and rated +1, +2, +3 and +4 according to the amount of disease. The total of the "plus" points of each group was then taken as the rating for that group.

On the basis of numbers of lesions by gross inspection the spleen ratings were 73 for group B, 46 for C and 14 for group D; the liver ratings, 58, 30 and 26, respectively.

On the basis of extent of disease estimated microscopically, the spleen ratings were 73 for group B, 60 for C and 36 for D; the liver ratings 64, 46 and 41, respectively; the ratings for all tracheobronchial lymph nodes,[3] 77, 57 and 30, respectively.

On the basis of extent of caseation estimated microscopically, the spleen ratings were 59 for group B, 45 for C and 15 for group D; the liver ratings 41, 34 and 20, respectively; the tracheobronchial lymph node ratings 59, 45 and 15, respectively.

Macroscopically negative were: one spleen in group B, 2 in group C and 14 in D; and the livers of 3 animals in group B, 10 in C and 14 in D.

Microscopically negative (2 sections from each tissue) were: spleens, none in group B, 2 in C and 3 in D; livers, none in B, 5 in C, 5 in D; tracheobronchial lymph nodes, none in B, 2 in C and 4 in D; inguinal lymph nodes, none in any group.

Weights of organs: Organ weight is expressed as per cent of body weight. Mean values for the spleens were 0.13 in 14 normal guinea pigs, 0.20 in group A1, 0.19 in A2, 0.49 in group B, 0.30 in C and 0.24 in D. Mean values for tracheo-

[3] Amount of disease in lymph nodes about the tracheal bifurcation was taken as a measure of lung infection.

bronchial lymph nodes were 0.02 in 14 normal animals, 0.02 in group A1, 0.02 in A2, 0.14 in B, 0.07 in C and 0.03 in group D. Mean values for the site of inoculation mass plus inguinal lymph nodes were 0.38 for group B, 0.41 for C and 0.75 for group D.

The mean weight per cent value of spleens was significantly greater statistically for group B than for groups C and D; the difference between the values of C and D was not significant. The mean value for tracheobronchial lymph nodes in group B was significantly greater than those in groups C and D; that of group C was significantly greater than that of D. On the other hand, the mean value for site of inoculation plus inguinal lymph nodes was significantly greater in group D than in groups B and C; the difference between C and B was not significant.

Composite rating: All data available were used to determine the position of each organ in an array of ascending values. For the spleen, microscopical information was considered most important, weight per cent next, macroscopical estimates least. For the liver, macroscopical rating was decisive, provided microscopical observation agreed. For the tracheobronchial nodes, weight per cent was considered most important, microscopical extent and caseation next. The arrays were divided into negative, +1, etc.

To obtain a single figure representing the visceral disease in each animal the total points for spleen, liver and tracheobronchial lymph nodes were added. The average number of points per animal were 9.6 for group B, 6.5 for C and 4.2 for group D.

These final evaluations are admittedly arbitrary. However, extensive correlations carried out by Mr. Frank Oechsli between the several measures of disease and the composite ratings suggested that our method of evaluation was justified.

Provided these data be subject to statistical analysis the differences between groups B and C, B and D, C and D are significant.

If the disease in animals of each of the 24 sets is compared, it is found that: the group B animal had more disease than that of C and D in 19 sets, more than C in 19 sets and more than the D animal in all of the 24 sets. The group C animal had more disease than the B animal in 3 sets, more than the D animal in 16 sets; D had more than C in 6 sets.

SUMMARY

1. Sulfanilamide causes marked or complete inhibition of tubercle bacillus cultural growth at a dilution of 1:1,000; sulfapyridine causes some inhibition at 1:5,000, complete at 1:1,000.

2. Guinea pigs treated with 340 mg. of drug divided into five daily doses showed blood levels of 10 to 30 mg. per cent falling off to lows of 1 to 5 mg. per cent during the night. Sulfanilamide levels rose more rapidly than those of sulfapyridine but were less well sustained at night.

3. Following infection with tubercle bacilli, the sulfanilamide and sulfapyridine treated animals were slower in the development of allergy than the controls.

4. There was distinctly less tuberculosis in the sulfanilamide and sulfapyridine

treated animals than in the controls; less in the sulfapyridine treated than in the sulfanilamide treated animals. These differences were shown by fewer and smaller tubercles in the visceral organs; less caseation in viscera and internal lymph nodes; and by smaller spleens and smaller internal lymph nodes.

5. The average arbitrary units of disease per animal were 9.6 for the controls, 6.5 for the sulfanilamide treated and 4.2 for the sulfapyridine treated group.

6. The local lesions, on the other hand, including sites of inoculation and inguinal lymph nodes were as large or larger in the treated than in the control groups.

SUMARIO

1. La sulfanilamida provoca inhibición pronunciada o completa de las colonias del bacilo tuberculoso a una dilución de 1:1,000; la sulfapiridina alguna inhibición a 1:5,000; completa a 1:1,000.

2. Los cobayos tratados con 340 mg. de droga, fraccionados en 5 dosis diarias, revelan cifras sanguíneas de 30 mg. que descienden de 1 a 5 mg.% durante la noche. El tenor de sulfanilamida se elevó mas rápidamente que el de sulfapiridina, pero no se sostuvo tan bien durante la noche.

3. Después de la infección con bacilos tuberculosos los animales tratados con sulfanilamida y sulfapiridina se mostraron más lentos en manifestar alergia que los testigos.

4. Hubo netamente menos tuberculosis en los animales tratados con sulfanilamida y sulfapiridina que en los testigos; y menos en los tratados con sulfapiridina que en los tratados con sulfanilamida. Esas diferencias se tradujeron por un número y tamaño menor de tubérculos en las vísceras y en los ganglios linfáticos internos.

5. El promedio de unidades arbitrarias de enfermedad por animal fué: 9.6 para los testigos, 6.5 para los tratados con sulfanilamida y 4.2% para los tratados con sulfapiridina.

6. En cambio las lesiones colaterales, incluyendo sitios de inoculación y ganglios linfáticos inguinales, revelaron el mismo tamaño y mayor en los grupos tratados que en los testigos.

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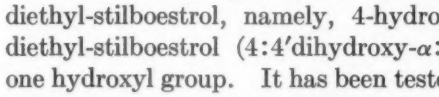
THE BACTERICIDAL ACTION OF STILBOESTROL ON TUBERCLE BACILLI[1]

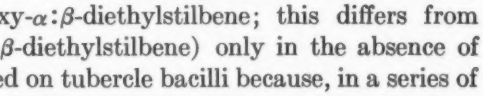
G. H. FAULKNER[2]

A previous communication (3), in which the bactericidal action of diethyl-stilboestrol on various types of microörganisms was described, contained a preliminary note concerning tubercle bacilli. It was there stated that contact of tubercle bacilli with stilboestrol in a concentration of 1 part in 5,000 for twenty-four hours *in vitro* caused the death of the organisms. The present paper presents the results of some further experiments with *Mycobacterium tuberculosis;* these have not been carried out on quite the same scale as those relating to other organisms owing to the necessity of using guinea pig inoculation to determine the survival of the tubercle bacilli, but they form a preliminary survey of the problem and are sufficient to enable several general conclusions to be drawn.

A few of these experiments relate to a compound very similar structurally to diethyl-stilboestrol, namely, 4-hydroxy-α:β-diethylstilbene; this differs from diethyl-stilboestrol (4:4′dihydroxy-α:β-diethylstilbene) only in the absence of one hydroxyl group. It has been tested on tubercle bacilli because, in a series of experiments (not yet published) in which the bactericidal activity of various compounds chemically related to stilboestrol was compared, it appeared to be active on some organisms in greater dilution than stilboestrol. It is one of a series of compounds examined for oestrogenic activity by Emmens (1, 2) (1940, 1942), who reports that it is much less active than stilboestrol in this respect when tested on ovariectomised mice.



4-hydroxy-α:β-diethylstilbene



4:4′-dihydroxy-α:β-diethyl-stilbene (diethyl-stilboestrol)

SOURCE OF MATERIALS AND MEDIA

The tubercle bacilli used have been obtained from material sent to the laboratory for routine investigation; they have been derived from milk and from human material, but the strains have not been typed. The bacilli have originated in various sources, comprising 15 sputa, 2 pleural fluids, one pus from a cervical gland, and 4 samples of milk. These materials underwent various preliminary processes before being used in these experiments. One sample of sputum was used without any preliminary treatment. Twelve sputa were subjected to preliminary digestion for thirty minutes by N sodium hydroxide, followed by centrifugalisation and neutralisation of the deposit. One sputum, after being

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digested as above, was sown on Loewenstein's medium and the resulting pure culture was used for the experiment. In 6 cases the material was derived from guinea pigs which had developed tuberculosis following routine diagnostic inoculation of milk (4 cases), of digested sputum (one case), and of pleural fluid (one case). In 4 of these animals the thick caseous pus was removed from the abscess which developed at the site of inoculation, and in 2 the enlarged spleens were removed and coarsely minced.

It will thus be seen that tubercle bacilli were obtained under various conditions —as a suspension of organisms previously treated with sodium hydroxide, as a suspension of a pure culture, distributed through pus, and embedded in small masses of spleen tissue. It was thought that the presence of pus or tissue might reduce the activity of the bactericide in two ways: the organic matter might exert an inhibiting action similar to that found to be produced by serum; moreover, the cells might exert a protective action on the bacilli by preventing the drugs from reaching them.

The bacilli were then incubated in a liquid medium containing the bactericide in the desired concentrations. The organisms were always divided among the various tubes of one experiment as equally as possible, and although absolute equality was not attained it was always certain that each tube received a massive inoculum.

The media used in this stage of the experiment were of three types, namely (*1*) nutrient medium (peptone water or broth) without serum; (*2*) nutrient medium containing 25 per cent of serum (in experiment 13 unfiltered guinea pig serum and in the others sheep serum passed through a Seitz filter); (*3*) human cerebrospinal fluid. The term "nutrient medium" is not strictly accurate when applied to tubercle bacilli and is merely intended to indicate that the media were at least favourable to survival of the organisms.

The two bactericides were dissolved in absolute alcohol, and this solution was subsequently added to the nutrient media immediately before use. The original alcoholic solutions were generally 1 per cent strength, but for making the higher concentrations a 2 per cent solution was used; the final concentration of absolute alcohol was therefore 4 per cent in the 1 in 1,250 dilution, and 1 per cent or 2 per cent in all other cases.

For controls, a volume of absolute alcohol equal to that of the alcoholic solution in the most highly concentrated experimental tube was added to the medium. Sterility tests of all experimental and control tubes were made.

EXPERIMENTAL METHODS

The experimental method has been similar to that used in the earlier experiments, namely, incubation at 37°C. for varying periods of time of the organisms suspended in nutrient media (generally in 10 cc. volumes) containing the bactericidal substances in concentrations varying between 1 part in 1,250 and 1 in 100,000, and subsequent determination whether the organisms have survived.

In previous experiments the mixture was subcultured on agar plates to demonstrate survival, but in the tubercle experiments the material after incubation was

inoculated into guinea pigs in order to determine whether the organisms had been killed or not. The purpose of the animal inoculation was simply to demonstrate the presence or absence of living tubercle bacilli in the medium which had been incubated *in vitro;* no attempt to modify the course of the induced disease in animals has been made.

The guinea pigs were inoculated subcutaneously ventrally with 2 cc. of the mixture after incubation. The weights of the animals were approximately 250 g., but varied between extremes of 200 and 320 g.; in any one experiment the weights were as similar as possible. After a lapse of between two and three weeks the control animals and any others in which an abscess was evident at the site of inoculation were killed; the rest were examined at intervals and killed whenever an abscess could be felt. Those showing no indication of being infected were left for varying periods up to a maximum of sixty-nine days—the time often being determined by the available food supply.

Every animal was examined after being killed; films were made from the local abscess and any other site appearing to be infected and examined for tubercle bacilli. Animals in which bacilli were found at the site of inoculation but in which no other macroscopical or microscopical evidence of tuberculosis was found are described in the tables as having local infections. Animals in which tubercle bacilli were found in the local abscess and at least one other site (for example, sternal or inguinal lymph nodes, spleen or lung) are described as having generalized tuberculosis. In one case (guinea pig 72) no local lesion could be found but tubercle bacilli were recovered from the inguinal node; this infection is considered as generalized. Variations in the extent of the infection in the animals with "generalized" tuberculosis are often apparent when performing the postmortem examinations but these cannot accurately be estimated and are not indicated in the summarized results. If these differences are taken into account, the effect is to show some slight reduction in some of the experimental animals compared with their controls (for example, guinea pig 40 with 42; 55 with 56; 72 and 73 with 74; and 83 with 84). Sometimes also the longer time taken for the experimental animals to show external evidence of infection suggests a reduction in the infecting dose in the experimental animal in comparison with its control, although finally both animals develop generalized infections.

Absence of signs of tuberculosis in these animals after five to seven weeks is not regarded as evidence of a completely negative result, or as proof that all the tubercle bacilli of the original inoculum were killed. It is, however, concluded that most of them have been killed, and perhaps all. In similar experiments with other organisms a difference between the number of organisms in an experimental tube compared with its control was sometimes due to the bacteriostatic action of the drug; in some concentrations the organisms survived but did not multiply, whereas in the control they did increase in numbers. In the case of tubercle bacilli multiplication could not take place under these conditions and differences between the experimental and control tubes must be caused by death of the organisms.

RESULTS AND CONCLUSIONS

The results of all the experiments are summarized in tables 1, 2 and 3. The experiment recorded briefly in the earlier paper is included in table 1; the animals concerned are numbers 1 to 6 of this series.

From the data given there, the following conclusions may be drawn.

Diethyl-stilboestrol and 4-hydroxy-diethylstilbene are bactericidal to tubercle bacilli *in vitro*. A complete comparison of the relative efficacy of the two compounds has not been achieved as the serial dilutions have not always been carried to the end point of activity; in the one case in which comparison can be made (experiment 22) the monohydroxy-diethylstilbene is approximately as good as the stilboestrol. The bactericidal activity of stilboestrol is reduced in the presence of organic matter (pus or serum). The activity of monohydroxy-diethylstilbene is reduced in the presence of pus; the effect of serum has not been quantitatively estimated.

The greatest dilution at which a bactericidal action has been recorded with stilboestrol is 1 in 100,000 in experiment 5, using digested sputum as the source of the organisms. The animal which received this material (guinea pig 23) showed absolutely no sign of disease after sixty-five days; when it was killed the uteri contained mature foetuses and the animal had increased in weight from 260 to 560 g. This was the highest dilution ever used and it may or may not have been the end point. These bacilli had previously been in contact with alkali, which might have modified their susceptibility to other drugs.

Monohydroxy-diethylstilbene is active against tubercle bacilli under these conditions in a dilution of at least 1 in 50,000 (experiment 14).

Tubercle bacilli (also from digested sputum) are killed within two hours by stilboestrol in a 1 in 5,000 concentration, but if a freshly made suspension of organisms in such a solution is injected, this is as highly infective as the control (experiment 3).

There are some discrepancies in the data concerning the action on tubercle bacilli in sputum after digestion, perhaps due to the fact that even after incubation with sodium hydroxide some sputa still remain somewhat mucoid; there seems to be very little action on undigested sputum (experiment 6) and an incomplete degree of digestion of some samples might, by preventing the substance from coming into contact with the organisms, account for the divergencies.

In the presence of 25 per cent serum the activity of stilboestrol on tubercle bacilli derived from digested sputum is reduced from approximately 1 in 100,000 to approximately 1 in 3,000 (1 in 5,000 was active in experiment 15, but not in experiment 13 or 16).

Tubercle bacilli (probably bovine) dispersed through guinea pig pus were killed by concentrations of 1 in 5,000, 10,000 and 20,000 of stilboestrol in experiments 7 and 8; however, using pus from a human pleural cavity in experiment 10, they were only partly killed by a concentration of 1 in 5,000. In both cases there was some reduction in the 1 in 50,000 tubes. This difference might have been due to the difference in the strain or to differences in the consistency of the pus. The monohydroxy-diethylstilbene has proved less

TABLE 1

Conditions under which diethyl-stilboestrol and 4-hydroxy-α:β-diethylstilbene are lethal to tubercle bacilli in vitro in aqueous media

EXPERIMENT NUMBER	SOURCE OF MATERIAL	BACTERICIDE	CONCENTRATION, 1 PART IN:	CONTACT AT 37°C.	EXPERIMENTAL GUINEA PIGS			CONTROL GUINEA PIGS		
					Evidence of tuberculosis	Day killed	Guinea pig number	Evidence of tuberculosis	Day killed	Guinea pig number
	Sputa (digested)									
3	1709	Stilboestrol	5,000	5 min.	General	22	15	General	21	18
	1709	Stilboestrol	5,000	2 hrs.	None	35	16			
9	2233	Stilboestrol	5,000	4½ hrs.	General	51	40	General	20	42
	2233	Stilboestrol	5,000	7 hrs.	None	51	41			
3	1709	Stilboestrol	5,000	20 hrs.	None	34	17	General	21	18
1	480	Stilboestrol	5,000	24 hrs.	None	37	1	General	37	2
	480	Stilboestrol	5,000	24 hrs.	None	37	3	General	37	4
	481	Stilboestrol	5,000	24 hrs.	None	37	5	General	37	6
2	1584	Stilboestrol	10,000	24 hrs.	None	34	11			
	1584	Stilboestrol	20,000	24 hrs.	None	34	12	General	23	14
	1584	Stilboestrol	50,000	24 hrs.	General	23	13			
5	1787	Stilboestrol	100,000	24 hrs.	None	65	23	General	20	24
14	3056	4-hy-d-s*	5,000	24 hrs.	None	50	57			
	3056	4-hy-d-s	20,000	24 hrs.	None	50	58	General	22	60
	3056	4-hy-d-s	50,000	24 hrs.	None	50	59			
	Sputum (not digested)									
6	1839	Stilboestrol	5,000	48 hrs.	Local	19	26	General	19	27
4	Minced spleen of guinea pig "A" (origin pleural fluid)	Stilboestrol	5,000	24 hrs.	None	47	19	General	25	20
		Stilboestrol	5,000	48 hrs.	None	69	21	General	24	22
7	Pus from abscess of guinea pig "B" (origin milk)	Stilboestrol	5,000	24 hrs.	None	36	28	Local	20	30
		Stilboestrol	5,000	48 hrs.	None	58	31	Local	21	33
		Stilboestrol	10,000	24 hrs.	None	36	29	Local	20	30
		Stilboestrol	10,000	48 hrs.	None	58	32	Local	21	33
8	Pus from abscess of guinea pig "C" (origin milk)	Stilboestrol	20,000	24 hrs.	None	52	35	Local	21	34
		Stilboestrol	20,000	48 hrs.	None	51	37	Local	20	39
		Stilboestrol	50,000	24 hrs.	Local	30	36	Local	21	34
		Stilboestrol	50,000	48 hrs.	Local	35	38	Local	20	39

* 4-hydroxy-diethylstilbene.

TABLE 1—*Continued*

EXPERIMENT NUMBER	SOURCE OF MATERIAL	BACTERICIDE	CONCENTRATION, 1 PART IN:	CONTACT AT 37°C.	EXPERIMENTAL GUINEA PIGS			CONTROL GUINEA PIGS		
					Evidence of tuberculosis	Day killed	Guinea pig number	Evidence of tuberculosis	Day killed	Guinea pig number
11	Pus from abscess of guinea pig "D" (origin milk)	4-hy-d-s	10,000	24 hrs.	General	23	48	General	23	51
		4-hy-d-s	20,000	24 hrs.	General	23	49			
		4-hy-d-s	100,000	24 hrs.	General	22	50			
10	Pus from pleural cavity	Stilboestrol	5,000	24 hrs.	Local	33	43	General	21	47
		Stilboestrol	50,000	24 hrs.	Local	24	44			
		4-hy-d-s	5,000	24 hrs.	Local	33	45			
		4-hy-d-s	50,000	24 hrs.	General	24	46			

TABLE 2

Conditions under which diethyl-stilboestrol and 4-hydroxy-α:β-diethylstilbene are lethal to tubercle bacilli in vitro in media containing 25 per cent serum

EXPERIMENT NUMBER	SOURCE OF MATERIAL	BACTERICIDE	CONCENTRATION, 1 PART IN:	CONTACT AT 37°C.	EXPERIMENTAL GUINEA PIGS			CONTROL GUINEA PIGS		
					Evidence of tuberculosis	Day killed	Guinea pig number	Evidence of tuberuulosis	Day killed	Guinea pig number
	Sputa (digested)									
17	3598	Stilboestrol	3,000	24 hrs.	None	46	67	Local	20	68
16	3571	Stilboestrol	5,000	24 hrs.	General	34	64	General	20	66
		Stilboestrol	10,000	24 hrs.	General	34	65			
13	2996	Stilboestrol	5,000	24 hrs.	General	23	55	General	23	56
15	3092	Stilboestrol	5,000	24 hrs.	None	49	61	General	21	63
		4-hy-d-s*	5,000	24 hrs.	None	49	62			
18	Pus from abscess of guinea pig "E" (origin sputum)	Stilboestrol	1,250	24 hrs.	None	46	70	General	20	71
		Stilboestrol	1,250	48 hrs.	General	45	73	General	19	74
		Stilboestrol	2,500	24 hrs.	Local	46	69	General	20	71
		Stilboestrol	2,500	48 hrs.	General	45	72	General	19	74
21	Pus from cervical gland	Stilboestrol	2,500	24 hrs.	None	26	82	General	26	84
		Stilboestrol	5,000	24 hrs.	General	26	83			
19	Minced spleen of guinea pig "F" (origin milk)	Stilboestrol	2,500	48 hrs.	General	20	77	General	20	78
		Stilboestrol	5,000	24 hrs.	General	21	75	General	21	76

* 4-hydroxy-diethylstilbene.

effective than stilboestrol in the presence of pus; it had no effect in a 1 in 10,000 concentration in experiment 11 on guinea pig pus (strain probably bovine) and was slightly less effective than stilboestrol in experiment 10 with the pus from a pleural cavity. The inferiority may be due to a lesser power of penetration than stilboestrol, as this compound was approximately as effective as stilboestrol when acting in cerebrospinal fluid.

In the presence of 25 per cent serum stilboestrol retains some of its activity against infected pus (experiments 18 and 21).

Stilboestrol was active against organisms of human origin enclosed in spleen tissue in a concentration of at least 1 in 5,000. In the presence of serum this con-

TABLE 3

Conditions under which diethyl-stilboestrol and 4-hydroxy-α:β-diethylstilbene are lethal to tubercle bacilli suspended in human cerebrospinal fluid

Experiment number	Source of material	Bactericide	Concentration, 1 part in:	Contact at 37°C.	Experimental guinea pigs			Control guinea pigs		
					Evidence of tuberculosis	Day killed	Guinea pig number	Evidence of tuberculosis	Day killed	Guinea pig number
20	Sputum (digested) 3762	Stilboestrol	2,500	24 hrs.	None	55	79	General	19	81
		Stilboestrol	5,000	24 hrs.	None	55	80			
22	Culture of sputum 4146	Stilboestrol	5,000	24 hrs.	None	28	85	General	15	93
		Stilboestrol	10,000	24 hrs.	None	28	86			
		Stilboestrol	20,000	24 hrs.	None	26	87			
		Stilboestrol	50,000	24 hrs.	General	26	88			
		4-hy-d-s*	5,000	24 hrs.	None	28	89			
		4-hy-d-s	10,000	24 hrs.	None	28	90			
		4-hy-d-s	20,000	24 hrs.	None	26	91			
		4-hy-d-s	50,000	24 hrs.	General	26	92			

* 4-hydroxy-diethylstilbene.

centration (and also 1 in 2,500) had no effect on organisms derived from milk in spleen tissue (experiment 19).

When tubercle bacilli were suspended in human cerebrospinal fluid there was apparently some reduction in the number of organisms in all the experimental tubes. It is not claimed that all the organisms were killed in any of the tubes, but apparently some were killed by a concentration of 1 in 50,000 of both substances, and most (if not all) by a 1 in 20,000 concentration.

In experiment 20 the tubercle bacilli had been previously in contact with alkali but in experiment 22 they were obtained from an actively growing culture. In both cases they were very numerous, and as 2 cc. were injected in all the animals the number of organisms introduced must have been large. In experiment 20 a film made from one loop of the inoculum showed very many organisms; in experi-

ment 22 they were left in clumps visible to the naked eye and not finely emulsifie l —with the intention of making conditions difficult rather than easy.

Comparison between the 3 animals in experiment 22 with "general infections" reveals differences between them. The control animal was killed on the fifteenth day because the ventral abscess was perforating the body wall; the spleen was enlarged and nodular, the inguinal nodes were enlarged and contained pus and the sternal nodes were enlarged. Tubercle bacilli were found in films from all four sites. Guinea pigs 88 and 92 (stilboestrol and monohydroxy-diethylstilbene 1 in 50,000) were killed on the twenty-sixth day. On the fifteenth day, when the control was killed, a very small nodule could be felt in animal 88 (stilboestrol) but no evidence of infection was found in animal 92. In the postmortem examination of 88 a small abscess was present in the skin and the spleen was enlarged and nodular; one sternal node and both inguinal nodes were enlarged. A few tubercle bacilli were found in films from all these sites. In 92 there was a small ventral abscess; the spleen and sternal nodes were not enlarged but the inguinal nodes were; tubercle bacilli were found in films from the site of inoculation, and a few in the inguinal nodes.

COMPARISON BETWEEN SUSCEPTIBILITY OF TUBERCLE BACILLI AND OF OTHER GRAM POSITIVE ORGANISMS TO STILBOESTROL

From all these results it appears that the susceptibility of tubercle bacilli to diethyl-stilboestrol is about the same as that of the other gram positive organisms. Results on other organisms with monohydroxy-diethystilbene have not yet been recorded and hence a comparison will not be made here.

As reported in the previous paper, the minimal lethal concentration for the gram positive organisms tested in nutrient aqueous media lies between 1 in 50,000 and 1 in 500,000; the corresponding figure for tubercle bacilli falls within this range. In the presence of 25 per cent serum a concentration of 1 in 2,500 kills *Staph. aureus*, and 1 in 5,000 kills *C. diphtheriae* and haemolytic streptococcus; the figure for tubercle bacilli given above is 1 in 3,000. When the gram positive organisms are suspended in filtered human serum a concentration of at least 1 in 1,250 is required to kill them; this accords with the results of experiments 18 and 21, in which much organic matter was present (pus and serum); in experiment 18 a concentration of 1 in 1,250 was probably on the borderline of activity (one animal being negative and one positive) and in experiment 21 a concentration of 1 in 2,500 was effective.

SUMMARY

Mycobacterium tuberculosis is killed by incubation *in vitro* in aqueous media containing diethyl-stilboestrol or 4-hydroxy-diethylstilbene.

The bactericidal activity on tubercle bacilli of both these compounds is reduced in the presence of organic matter.

This investigation is being continued by therapeutic trials on tuberculous guinea pigs.

SUMARIO

El Mycobacterium tuberculosis es destruído por la incubación *in vitro* en medios acuosos que contienen dietil-estilbestrol o 4-hidroxi-dietilestilbeno.

En presencia de materia orgánica disminuye la actividad bactericida de ambos compuestos sobre los bacilos tuberculosos.

Continúase esta investigación con pruebas terapéuticas en cobayos tuberculosos.

I wish to thank Doctor A. I. Messer and Professor J. H. Gaddum for continued help during the progress of this investigation; also to acknowledge my indebtedness to Professor E. C. Dodds for the 4-hydroxy-diethylstilbene, and to Messrs. Boots Pure Drug Co. for the stilboestrol.

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BRIEF REPORTS

TRACHEOTOMY FOR TUBERCULOUS LARYNGEAL STENOSIS[1]

EMIL ROTHSTEIN AND H. B. PIRKLE

Tuberculosis of the larynx is frequent as a complication of pulmonary tuberculosis. It is seen most often in patients with cavitation and positive sputum, and, according to Lederer (1), is found at autopsy in the majority of these cases, varying in incidence from 50 to 80 per cent. A characteristic feature of healing in tuberculosis is the formation of dense scar tissue and this is true in the larynx as elsewhere. If both vocal cords are affected as well as the anterior and posterior commissures, a ring of scar tissue is formed which, upon contraction, would result in narrowing the air passage.

CASE REPORT

H. S., a white female, was born in 1910 and became ill with tuberculosis in 1937; her laryngeal symptoms were the first to appear. She was admitted to the Indiana State Sanatorium July 30, 1940, with X-ray evidence of far advanced bilateral pulmonary tuberculosis without cavitation. The sputum was positive for tubercle bacilli (Gaffky III). Indirect laryngoscopy showed that the arytenoids were markedly thickened, swollen and reddened. Both cords were thickened, roughened and moderately oedematous; there was marked interarytenoid fulness and congestion of epiglottis.

Left artificial pneumothorax was started October 2, 1940. The sputum became negative (twenty-four hour specimens by concentration) on December 4, 1940 and remained so for about one year, then it was occasionally positive (Gaffky II).

In March, 1942 a right phrenic crush was performed. In July, 1942 special films (oblique views with grid) were interpreted as revealing multiple small cavities in the right upper lobe and bilateral pneumothorax was considered; its induction was to be delayed until the paralyzed right diaphragm had regained its motion. At this time examination of the larynx by indirect laryngoscopy revealed considerable stenosis due to fusion of the anterior ends of the vocal cords. On October 19, 1942 she complained of increasing aphonia, stridor and dyspnoea. Direct laryngoscopy revealed an oval orifice whose greatest diameter was 5 mm.; this was impassable to an adult-size bronchoscope. After the attempted passage of the bronchoscope the dyspnoea and cyanosis became more extreme and, just prior to the tracheotomy, the patient was in collapse and apparently *in extremis*. Tracheotomy was performed at the Robert Long Hospital, October 19, 1942, and she returned to our institution on October 24, 1942 with the tracheotomy tube *in situ*. At first much difficulty was experienced as the tube would become blocked with sputum which she could not expectorate. It was necessary to have a machine for suction in her room at all times and she would pass a catheter through the tracheotomy tube at frequent intervals. As time went on and as a result of improvement in her lungs this became necessary less frequently so that after a few months she could expectorate without use of the suction apparatus.

Right artificial pneumothorax was started on February 8, 1943 and is being continued to the present, March 6, 1944. Her sputum has been negative on smear (twenty-four

[1] From the Indiana State Sanatorium, Rockville, Indiana.

and seventy-two hour specimens, by concentration) from April 28, 1943 and on culture from July 27, 1943 to the present date, March 8, 1944. Examination of the larynx reveals a condition essentially unchanged, with a 5 mm. orifice still present.

Her X-ray films reveal marked improvement of both lungs. On the right is an artificial pneumothorax, chiefly over the upper lobe, with about 30 per cent collapse. No cavitation or consolidation can be seen. On the left is an artificial pneumothorax over the upper lobe, with atelectasis of the collapsed portion. No cavitation is seen. This roentgenological picture has been present since April 30, 1943. The patient is now on two hours' walking exercise daily, and has been so from January 1, 1944. The complete diagnosis is:

1. Pulmonary tuberculosis arrested, with bilateral collapse therapy.
2. Bilateral artificial pneumothorax.
3. Tuberculosis of the larynx with stenosis.
4. Status posttracheotomy with tracheotomy tube *in situ*.

DISCUSSION

Tracheotomy was advocated as a therapeutic procedure in tuberculosis of the larynx to spare this organ from the passage of air, but it soon fell into disrepute. Most authors considered it a prelude to the patient's exitus. Very few cases have been reported in whom a condition of arrest occurred after tracheotomy for tuberculous stenosis of the larynx; in none have we been able to find bilateral pneumothorax successfully used with tracheotomy tube *in situ*. Stevenson (2) has seen but one case needing tracheotomy for tuberculous stenosis of the larynx. Dr. Max Pinner (3) writes that he has seen but one case. Dr. Gordon B. New (4) writes, "I can recall offhand only about a half dozen such cases." The largest series of cases was reported by Myerson (5) from Sea View Hospital. Of 9 cases requiring tracheotomy only 3 survived. Apparently none of these received collapse therapy. Myerson discusses a problem that was serious in our patient—difficulty in expectorating profuse sputum. This was cared for in our case by the use of a suction apparatus, with passage of a catheter into the tracheotomy tube by the patient as often as every hour. As pneumothorax on the right side was administered with collapse of the upper lobe the amount of sputum markedly decreased and the patient was soon able to expectorate without any difficulty. Thomson (6), in his ten years' experience with 477 cases of laryngeal tuberculosis, saw 3 cases requiring tracheotomy. Wilkinson (7) reported one case. Woodward (8) reported 3 cases.

Our patient presents two unique features. The first of these is the use of periodic suction to aid the expectoration of excessive sputum. The other is the use of the usual type of collapse therapy in spite of the presence of the tracheotomy tube. This course of therapy is apparently bearing dividends. The patient's condition is classified as arrested. The X-ray films reveal no cavitation in either collapsed lung, the sputum is negative on smear (seventy-two-hour concentrated specimens) and on culture (since July, 1943) and the prognosis now begins to look guardedly good.

Now that the lung lesion is arrested reconstructive laryngeal surgery is being considered. Doctor New of the Mayo Clinic (9) has suggested excising some of the stenotic tissue and replacing it with a skin graft, and the temporary

use of a prosthesis made of vernonite with the ultimate closure of the tracheotomy wound.

SUMMARY

A patient with pulmonary tuberculosis is presented with bilateral pneumothorax and laryngeal tuberculosis in whom laryngeal stenosis developed, requiring tracheotomy. As a result of therapy the patient's condition has become arrested.

SUMARIO

Preséntase un enfermo de tuberculosis pulmonar con neumotórax bilateral y tuberculosis laríngea, en el que se presentó estenosis de la laringe que exigió la traqueotomía. Con la terapéutica aplicada se estacionó el estado del enfermo.

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PLEURAL CHANGES IN OLEOTHORAX[1]

PETER A. HERBUT AND ROBERT CHARR

The purpose of the present communication is to report briefly the postmortem findings in a case of oleothorax with a reference to the effect of mineral oil upon the pleura.

A white female, aged twenty-nine, was diagnosed tuberculous in 1935. The lesions appeared exudative in the roentgenograms and were located in the right upper lobe. The sputum contained numerous tubercle bacilli. After a trial period of bed-rest, artificial pneumothorax was begun on the right side. The collapse was satisfactory for six months, after which effusion developed. The fluid was aspirated on several occasions and gradually was replaced with sterile mineral oil. The pulmonary symptoms subsided, and the sputum became negative for tubercle bacilli. The patient remained in fair health until 1943, when she developed tuberculous meningitis and died.

The roentgenogram (figure 1) taken shortly before death showed an oleothorax on the right side with scattered tubercles throughout both lungs.

Postmortem findings: The upper and lateral portions of the right pleural cavity contained a single loculated space which measured 14 x 10 x 3 cm. It was filled with an oily, light brown, turbid fluid. Oil droplets were well seen when some of the fluid was placed in a basin of water. The lining of the pleura was gray, rather smooth and for the most part glistening. Both the visceral and parietal layers were greatly thickened, each measuring as much as 8 mm. in thickness. Each was composed of extremely firm, homogeneously grayish-white, dense fibrous tissue which ended abruptly at its junction with the underlying structures. The remaining portion of the right pleural cavity and all of the left pleural cavity were completely obliterated with dense, fibrous adhesions. The entire surface was light gray to pink, smooth and showed no caseation. The remaining portions of both lungs together with the spleen, liver and kidneys contained numerous miliary tubercles. Some of the cervical, mediastinal and mesenteric lymph nodes were surrounded with fibrous tissue capsules and centrally were completely caseous. There were tuberculous ulcers in the lower ileum, the caecum and ascending colon.

Microscopical sections of many portions of the right visceral and parietal pleura disclosed that two-thirds of the immediately subjacent pleura was composed of irregularly arranged masses and bands of pink staining collagenous fibrous tissue (figure 2). They were completely devoid of nuclei but contained between their fibres many empty, spherical spaces. Around the periphery of some of the latter, there were deposits of minute or large, bluish stained globules. Nowhere in this zone were there capillaries, inflammatory cells, phagocytes or giant cells. There were, however, scattered, small, focal collections of loose, connective tissue which contained a few capillaries and occasional round cells with scanty cytoplasm. The remaining third of the pleura was composed of bands of collagenous fibrous tissue loosely arranged in parallel lamina and producing between the fibres a meshwork of empty spaces. Many of the fibres still contained a few elongated, flat nuclei. Scattered throughout, there were thin and thick-walled capillaries and occasional round cells with scanty cytoplasm. The innermost layers of the pleura, just outside the lung parenchyma, contained small and large arterioles. The walls of some of the latter

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were so thick that the lumina were reduced to mere slits or were entirely obliterated. The fibrous tissue always ended abruptly at the junction of the pleura with the lung parenchyma. In the latter, immediately adjoining the pleura, there were many scattered miliary tubercles, but between these the alveoli showed no more fibrosis than they did else-

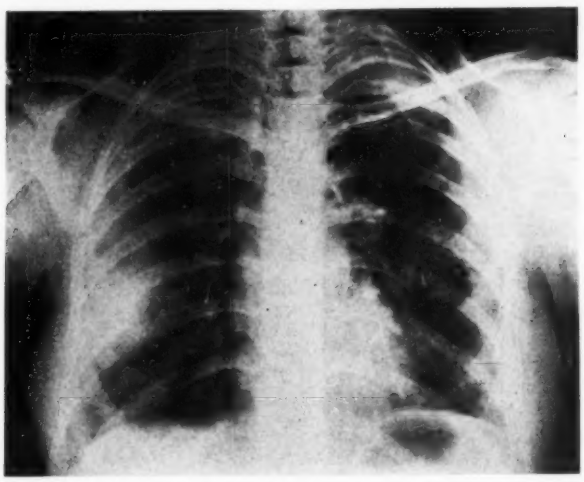

FIG. 1. Oleothorax on the right side: scattered tubercles throughout the remainder of the right lung and the left lung

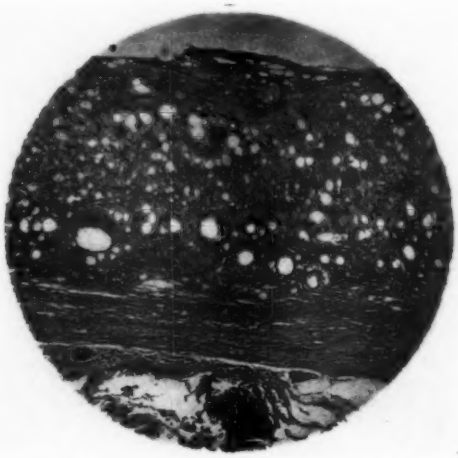

FIG. 2. A section of the right visceral pleura showing from without inward a broad zone of loose, vacuolated, collagenous fibrous tissue; a zone of dense, lamellated fibrous tissue; two small thick-walled arterioles and a tubercle in the otherwise uninvolved lung parenchyma. Haematoxylin and eosin: × 19.

where in the lung. A strip of the entire right upper lobe from the periphery to the hilum was cut into seven blocks and sections of each were examined. They all contained miliary tubercles similar to those in other portions of both lungs. None showed any increase in fibrous tissue or deposits of fat globules or blue spheres such as were seen in the pleura.

Nile-blue sulphate stains of the pleura disclosed pink staining globules filling the spherical spaces between the collagenous bands of the outer two-thirds. Alternate sections stained with osmic acid failed to take a black stain. Sections of the lung parenchyma of the right upper lobe and of the draining mediastinal lymph nodes stained with Nile-blue sulphate showed only a peppery deposit of bluish granules about some of the tubercles.

Sections of other organs disclosed fibrocaseous tuberculosis of the cervical, mediastinal and mesenteric lymph nodes, lungs and spleen, and miliary tuberculosis of the lungs, mediastinal lymph nodes, spleen, liver, adrenals, pancreas, kidneys, bone marrow and fallopian tubes.

Both smears and cultures of lung tissue were positive for tubercle bacilli.

SUMMARY

In the case reported, the mineral oil was in the right pleural cavity for seven years. Other than pleural thickening, there was nothing to suggest that the mineral oil had any effect upon the pleural surface. The spherical globules between the meshes of the collagenous fibrous tissue of the pleura were identified as droplets of mineral oil by the method suggested by Kaplan (1).

SUMARIO

En el caso aquí descrito el aceite mineral había permanecido por espacio de siete años en la cavidad pleural derecha. Aparte del espesamiento nada más indicaba que el aceite hubiera ejercido el menor efecto sobre la superficie pleural. Los glóbulos esféricos situados entre las mallas del tejido fibroso colágeno fueron identificados como gotillas de aceite mineral conforme al método indicado por Kaplan (Nota 1).

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The American Trudeau Society, the Medical Section of the National Tuberculosis Association, met in Chicago, Illinois, on May 10, 1944. New officers and Council members were elected by the three hundred members present at the meeting.

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